26 October 2017
EMA/PRAC/782068/2017
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 25-29 September 2017

Chair: June Raine – Vice-Chair: Almath Spooner

Health and safety information

In accordance with the Agency's health and safety policy, delegates were briefed on health, safety and emergency information and procedures prior to the start of the meeting.

Disclaimers

Some of the information contained in the minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scope listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also change during the course of the review. Additional details on some of these procedures will be published in the PRAC meeting highlights once the procedures are finalised.

Of note, the minutes are a working document primarily designed for PRAC members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006, Rev. 1).

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1. Introduction

1.1. Welcome and declarations of interest of members, alternates and experts

The Chairperson opened the 25-29 September 2017 meeting by welcoming all participants.

Based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some Committee members in upcoming discussions; in accordance with the Agency's policy on the handling of conflicts of interests, participants in this meeting were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion (Annex II – List of participants). No new or additional conflicts were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 24 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC Chairperson noted that Daniela Philadelphy was replacing Marianne Lunzer, as the new alternate for Austria. The PRAC Chairperson also announced that Torbjorn Callreus was to step down as PRAC alternate for Denmark after the current PRAC plenary meeting. The PRAC thanked him for his contribution to the work of the Committee.

1.2. Agenda of the meeting on 25-29 September 2017

The agenda was adopted with some modifications upon request from the members of the Committee and the EMA secretariat.

1.3. Minutes of the previous meeting on 29 August-1 September 2017

The minutes were adopted with some amendments received during the consultation phase and will be published on the EMA website.

Post-meeting note: the PRAC minutes of the meeting held on 29 August-1 September 2017 were published on the EMA website on 20 October 2017 (EMA/PRAC/701894/2017).

2. EU referral procedures for safety reasons: urgent EU procedures

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

3. EU referral procedures for safety reasons: other EU referral procedures

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Daclizumab - ZINBRYTA (CAP) – EMEA/H/A-20/1456

Applicant(s): Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia; PRAC Co-rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Review of the benefit-risk balance following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004 based on pharmacovigilance data

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for Zinbryta (daclizumab) indicated for the treatment of relapsing forms of multiple sclerosis (RMS), in order to further investigate the risk of liver injury and assess its impact on the benefit-risk balance of the medicinal product. The review was initiated following cases of serious liver injury, including a fatal case of fulminant liver failure. In July 2017, the PRAC recommended provisional measures without prejudice to the final conclusions of the ongoing procedure. For further background and information on the provisional measures, see PRAC minutes June 2017, PRAC minutes July 2017 and PRAC minutes September 2017.

Summary of recommendation(s)/conclusions

The PRAC discussed a draft list of experts (LoE) for the Scientific Advisory Group (SAG) on neurology (SAG-N) meeting scheduled on 12 October 2017.

Post-meeting note: on 9 October 2017, the PRAC adopted by written procedure the LoE for the SAG-N.

3.2.2. Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); enoxacin (NAP); flumequin (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP);

prulifloxacin (NAP); rufloxacin (NAP)
Quinolones for systemic and inhalation use: cinoxacin (NAP); nalidixic acid (NAP); pipemidic acid (NAP) - EMEA/H/A-31/1452

Applicant(s): Raptor Pharmaceuticals Europe BV (Quinsair), various

PRAC Rapporteur: Eva Jirsová; PRAC Co-rapporteur: Martin Huber

Scope: Review of the benefit-risk balance following notification by Germany of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for quinolone- and fluoroquinolone-containing medicines for systemic and inhalational use, indicated for the treatment of bacterial infections, in particular those which are serious and life-threatening, in order to assess the persistence of side effects known to occur with quinolone and fluoroquinolone antibiotics, following reports of long-lasting side effects mainly affecting musculoskeletal and nervous systems. The ongoing review also assesses the need for adequate and consistent risk minimisation measures (RMMs) and the impact of this safety concern if confirmed on the overall benefit risk balance of quinolones and fluoroquinolones for systemic and inhalational use especially in authorised indications which are related to treatment of non-serious/non severe infections. For further background, see PRAC minutes February 2017 and PRAC minutes June 2017.

Summary of recommendation(s)/conclusions

The PRAC discussed the assessment reports prepared by the Rapporteurs as well as a draft list of outstanding issues (LoOI) to be addressed by the MAHs.

Post-meeting note: on 6 October 2017, the PRAC adopted by written procedure the LoOI to the MAHs. On 16 October 2017, PRAC also adopted by written procedure a revised timetable for the procedure (EMA/PRAC/38618/2017 Rev. 3).

3.2.3. Valproate and related substances: sodium valproate, valproic acid, valproate semisodium, valpromide (NAP) - EMEA/H/A-31/1454

Applicant(s): Sanofi-aventis, various

PRAC Rapporteur: Sabine Straus; PRAC Co-rapporteur: Jean-Michel Dogné

Scope: Review of the benefit-risk balance following notification by France of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for medicinal products containing valproate and related substances indicated for the treatment of bipolar disorder, epilepsy and in some Member States for the treatment of migraine, in order to assess the evidence in support of a contraindication in the treatment of bipolar disorder during pregnancy and in women of childbearing potential who are not on effective contraception, and to review the effectiveness of the current risk minimisation measures (RMMs) across all indications. For further background, see PRAC minutes March 2017, PRAC minutes June 2017, PRAC minutes July 2017 and PRAC minutes September 2017.

Summary of recommendation(s)/conclusions

The PRAC adopted a revised list of questions (LoQ) for the stakeholders meeting to be held on 13 October 2017 as well as an updated timetable (EMA/PRAC/154221/2017 rev 2) for the procedure. In addition, the PRAC discussed a draft list of experts (LoE) for the Scientific Advisory Group (SAG) on neurology (SAG-N) and a draft LoE for the SAG on psychiatry (SAG-P), both scheduled on 12 October 2017.

Furthermore, the PRAC held its first public hearing on 26 September 2017. Further information, including the agenda, written interventions, a summary report and the video recording are available on the dedicated webpage for the public hearing.

Post-meeting note: On 9 October 2017, the PRAC adopted a LoQ to the EMA working group on quality review of documents (QRD) to take place on 19 October 2017. On 11 October 2017, the PRAC also adopted by written procedure the LoE for the SAG-N meeting and the LoE for the SAG-P meeting.

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[1]

3.4.1. Paracetamol[2] (NAP); paracetamol, tramadol[2] (NAP) - EMEA/H/A-31/1445

Applicant(s): GlaxoSmithKline Consumer Healthcare AB (Alvedon 665 mg modified-release tablet), various

PRAC Rapporteur: Željana Margan Koletić; PRAC Co-rapporteur: Adam Przybylkowski

Scope: Request for re-examination under Article 32 of Directive 2001/83/EC of review of the benefit-risk balance of modified release paracetamol-containing products following notification by Sweden of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

Following the PRAC recommendation adopted at the September 2017 PRAC meeting[3], to suspend the marketing authorisations of modified release paracetamol-containing products, two marketing authorisation holders (MAHs) concerned by this referral procedure requested a re-examination. For further background, see PRAC minutes July 2016, PRAC minutes November 2016, PRAC minutes February 2017, PRAC minutes March 2017, PRAC minutes July 2017 and PRAC minutes September 2017.

Upon receipt of the grounds for re-examination from two MAHs concerned by this referral procedure, the PRAC will initiate a re-examination procedure[4], expected to conclude at the December 2017 PRAC meeting (scheduled on 27-30 November 2017).

Discussion

The PRAC noted the notification letters from two of the MAHs concerned by this referral

[1] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[2] Modified release formulations only
[3] Held on 29 August-1 September 2017
[4] Under Article 32 of Directive 2001/83/EC

procedure to request a re-examination of the recommendation adopted by the PRAC at its September 2017 meeting.

The PRAC appointed Željana Margan Koletić as Rapporteur and Adam Przybylkowski as Co-Rapporteur for the re-examination procedure.

Summary of recommendation(s)/conclusions

The Committee agreed on a preliminary timetable (EMA/PRAC/460935/2016 Rev.2) for the re-examination procedure expected to conclude at the December 2017 PRAC meeting (scheduled on 27-30 November 2017). The timetable will be finalised further to the receipt of the MAHs' grounds for re-examination of the PRAC recommendation.

3.5. Others

None

4. Signals assessment and prioritisation[5]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Apixaban – ELIQUIS (CAP); dabigatran – PRADAXA (CAP); edoxaban – LIXIANA (CAP); rivaroxaban – XARELTO (CAP)

Applicant(s): Bayer AG (Xarelto); Boehringer Ingelheim International GmbH (Pradaxa); Bristol-Myers Squibb- Pfizer EEIG (Eliquis); Daiichi Sankyo Europe GmbH (Lixiana)

PRAC Rapporteur: Menno van der Elst

Scope: Signal of cholesterol embolism

EPITT 19078 – New signal

Lead Member State(s): NL, SE, DK, UK

Background

Dabigatran is a direct thrombin inhibitor indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) under certain conditions, as well as for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. Apixaban, edoxaban and rivaroxaban are direct factor Xa inhibitors. They are indicated for the prevention of stroke and systemic embolism in adult patients with NVAF under conditions as well as for the treatment of DVT and PE, and the prevention of recurrent DVT and PE in adults.

The exposure for Xarelto, a centrally authorised medicine containing rivaroxaban, is estimated to have been approximately 16,136,527 patient-years worldwide, in the period

[5] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

from first authorisation in 2008 to 2016. The exposure for Pradaxa, a centrally authorised medicine containing dabigatran, is estimated to have been approximately 7,334,621 patient-years worldwide, in the period from first authorisation in 2008 to 2017. Eliquis, a centrally authorised medicine containing apixaban, is estimated to have been used by more than 5,350,032 patients worldwide, in the period from 2011 to 2016. Lixiana, a centrally authorised medicine containing edoxaban, is estimated to have been used for 260,310 patient-years for atrial fibrillation and venous thromboembolisms and by 437,431 patients in the orthopaedic surgery indication from 22 April 2011 until 31 December 2016 worldwide.

During routine signal detection activities, a signal of cholesterol embolism was identified by the Netherlands, based on 2 case reports of a direct oral anticoagulant possibly associated with cholesterol embolism retrieved from the Netherlands Pharmacovigilance centre (Lareb) database and a further 13 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and supported requesting a comprehensive cumulative review of events of 'fat embolism', 'atheroembolism', 'microembolism' and 'blue toe syndrome' and related terms in association with dabigatran, apixaban, edoxaban or rivaroxaban with a view to amending the product information and/or the RMP as applicable.

The PRAC appointed Menno van der Elst as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for Pradaxa (dabigatran), Eliquis (apixaban), Lixiana (edoxaban) and Xarelto (rivaroxaban) should submit to EMA, within 60 days, a cumulative review of the signal including an analysis of all case reports of 'fat embolism', 'atheroembolism', 'microembolism' and 'blue toe syndrome' and related terms in association with dabigatran, apixaban, edoxaban or rivaroxaban, and a proposal for amending the product information and/or the RMP.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

4.2.1. Gonadotropin-releasing hormone (GnRH) agonists: Buserelin (NAP); goserelin (NAP); leuprorelin (NAP); triptorelin (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of thromboembolic events

EPITT 19084 – New signal

Lead Member State(s): DE, IT, SE

Background

Gonadotropin-releasing hormone (GnRH) agonists are drugs that bind to the GnRH receptors located in the pituitary gland. They are used in various indications including the treatment of prostate cancer.

Following several publications describing an increased risk of thromboembolic events in prostate cancer patients treated with GnRH agonists, in particular *Ehdaie et al., 2012*[6], *Klil-Drori et al., 2016*[7] and *O'Farrell et al., 2016*[8], taking also into account several published postulated mechanisms regarding an association of endocrine treatment and thromboembolic disease (*Winkler, et al., 1996*[9]; *Li et al., 2007*[10] *Martinez et al., 2016*[11]), a signal of thromboembolic events was identified by Germany, suggesting that GnRH agonists may contribute to thromboembolic events in patients treated for prostate cancer. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of thromboembolic events from the literature with GnRH agonist-containing products. Having considered the available evidence from the literature, the PRAC acknowledged the limitations of the currently available data. The association between GnRH agonists and thromboembolic events observed in epidemiological studies cannot be sufficiently delineated from an association between prostate cancer and thromboembolic events due to possible confounding by indication and disease severity. Therefore the PRAC considered that the strength of the available evidence supporting an association between GnRH agonists and thromboembolic events in patients with prostate cancer was limited in light of the current knowledge.

The PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The PRAC agreed that MAHs for GnRH agonists: buserelin-, goserelin-, leuprorelin- and triptorelin-containing products should continue to monitor the association of thromboembolic events in patients with prostate cancer as part of routine safety surveillance.

4.3. Signals follow-up and prioritisation

4.3.1. Acetazolamide (NAP)

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of acute generalised exanthematous pustulosis (AGEP)

[6] Ehdaie B, Atoria CL, Gupta A, et al. Androgen deprivation and thromboembolic events in men with prostate cancer.cancer. 2012;118(13):3397-3406. doi:10.1002/cncr.26623
[7] Klil-Drori AJ, Yin H, Tagalakis V, Aprikian A, Azoulay L. Androgen deprivation therapy for prostate cancer and the risk of venous thromboembolism. Eur Urol. 2016 Jul;70(1):56-61. doi: 10.1016/j.eururo.2015.06.022
[8] O'Farrell S, Sandström K, Garmo H, Stattin P, Holmberg L, Adolfsson J, Van Hemelrijck M. Risk of thromboembolic disease in men with prostate cancer undergoing androgen deprivation therapy. BJU Int. 2016 Sep;118(3):391-8. doi: 10.1111/bju.13360
[9] Winkler UH. Effects of androgens on haemostasis. Maturitas. 1996 24:147-155
[10] Li S, Li X, Li J, Deng X, Li Y. Inhibition of oxidative-stress-induced platelet aggregation by androgen at physiological levels via its receptor is associated with the reduction of thromboxane A2 release from platelets. 2007. Steroids. 72:221-230
[11] Martinez C, Suissa S, Rietbrock S, Katholing A, Freedman B, Cohen AT, Handelsman DJ. Testosterone treatment and risk of venous thromboembolism: population based case-control study. BMJ. 2016. 30;355:i5968

EPITT 18892 - Follow-up to May 2017

Background

For background information, see PRAC minutes May 2017.

The MAH replied to the request for information on the signal of acute generalised exanthematous pustulosis (AGEP) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of AGEP associated with acetazolamide, the PRAC agreed that the product information of acetazolamide-containing medicinal product(s) should be amended to include a warning on the possibility of occurrence of AGEP at treatment initiation as well as to add AGEP as an undesirable effect with an unknown frequency.

Summary of recommendation(s)

- The MAH(s) for acetazolamide-containing medicinal product(s) should submit to EMA or to the national competent authorities of the MSs, as applicable, within 60 days, a variation for amending the product information[12].

For the full PRAC recommendation, see EMA/PRAC/610975/2017 published on 23/10/2017 on the EMA website.

4.3.2. Azithromycin (NAP); clarithromycin (NAP); erythromycin (NAP); roxithromycin (NAP)

Applicant(s): various

PRAC Rapporteur: Almath Spooner

Scope: Signal of acute generalised exanthematous pustulosis (AGEP)

EPITT 18891 - Follow-up to May 2017

Background

For background information, see PRAC minutes May 2017.

The MAHs replied to the request for information on the signal of acute generalised exanthematous pustulosis (AGEP) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of AGEP associated with clarithromycin, erythromycin, azithromycin and roxithromycin, the PRAC agreed that the product information of clarithromycin-, erythromycin-, azithromycin- and roxithromycin-containing medicinal products should be amended to include a warning on the possibility of occurrence of severe cutaneous adverse reactions (SCARs) including AGEP and related precautions for use, as well as to add AGEP as an undesirable effect with an unknown frequency.

Summary of recommendation(s)

[12] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

- The MAHs for clarithromycin-, erythromycin-, azithromycin- and roxithromycin-containing medicinal products should submit to EMA or to the national competent authorities of the MSs as applicable, within 60 days, a variation for amending the product information[13].

For the full PRAC recommendation, see EMA/PRAC/610975/2017 published on 23/10/2017 on the EMA website.

4.3.3. Cladribine - LITAK (CAP) - EMEA/H/C/000504/SDA/025; NAP

Applicant(s): Lipomed GmbH, various

PRAC Rapporteur: Patrick Batty

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 18875 – Follow-up to May 2017

Background

For background information, see PRAC minutes May 2017.

The MAHs replied to the request for information on the signal of progressive multifocal leukoencephalopathy (PML) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, the PRAC agreed that the product information of cladribine-containing products authorised for oncology indications should be amended to include a special warning and precautions for use in relation to the risk of PML.

Summary of recommendation(s)

- The MAHs for cladribine-containing products authorised for oncology indications should submit to EMA or to the national competent authorities of the MSs as applicable, within 60 days, a variation for amending the product information[14].
- Moreover, the MAHs should consider PML as a potential risk in the RMP and PSUR and follow up appropriately.
- The MAHs should inform healthcare professionals of these changes via a direct healthcare professional communication (DHPC). The PRAC reviewed and agreed with the content of the DHPC and the communication plan, due for further agreement by CHMP.

For the full PRAC recommendation, see EMA/PRAC/610975/2017 published on 23/10/2017 on the EMA website.

4.3.4. Desloratadine – AERINAZE (CAP) – EMEA/H/C/000772/SDA/016, AERIUS (CAP) - EMEA/H/C/000313/SDA/067, AZOMYR (CAP) - EMEA/H/C/000310/SDA/067, DASSELTA (CAP) - EMEA/H/C/002310/SDA/003, DESLORATADINE ACTAVIS (CAP) - EMEA/H/C/002435/SDA/003, DESLORATADINE RATIOPHARM (CAP) - EMEA/H/C/002404/SDA/003, DESLORATADINE TEVA (CAP) -

[13] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly
[14] Update of SmPC section 4.4. The package leaflet is to be updated accordingly

EMEA/H/C/002419/SDA/003, NEOCLARITYN (CAP) - EMEA/H/C/000314/SDA/067; loratadine (NAP)

Applicant(s): Merck Sharp & Dohme Limited (Aerinaze, Aerius, Azomyr), Actavis Group PTC ehf (Desloratadine Actavis), Krka, d.d., Novo mesto (Dasselta), Ratiopharm GmbH (Desloratadine Ratiopharm), Teva B.V. (Desloratadine Teva); various

PRAC Rapporteur: Laurence de Fays

Scope: Signal of weight increase in children

EPITT 18906 – Follow-up to July 2017

Background

For background information, see PRAC minutes July 2017.

The MAHs replied to the request for information on the signal of weight increase in children and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, and the known role of histamine H1 receptors in mediating energy intake and expenditure, the PRAC agreed that the product information of loratadine- and desloratadine-containing medicinal products should be amended to add, respectively, weight increased as an undesirable effect of unknown frequency, and weight increased as well as increased appetite as undesirable effects of unknown frequency.

Summary of recommendation(s)

- The MAHs of loratadine- and desloratadine-containing medicinal products should submit to EMA or to the national competent authorities of the MSs as applicable, within 60 days, a variation for amending the product information[15].

For the full PRAC recommendation, see EMA/PRAC/610975/2017 published on 23/10/2017 on the EMA website.

4.3.5. Doxycycline (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of doxycycline induced Jarisch-Herxheimer reaction

EPITT 18937 – Follow-up to September 2017

Background

For background information, see PRAC minutes September 2017.

The MAHs replied to the request for information on the signal of doxycycline-induced Jarisch-Herxheimer reaction and the responses were assessed by the Rapporteur.

Discussion

[15] Update of SmPC section 4.8. The package leaflet is to be updated accordingly

Having considered the available evidence in EudraVigilance and in the literature, and the known association of doxycycline with Jarisch-Herxheimer reaction, the PRAC agreed that the product information of doxycycline-containing medicinal products should be amended to include a special warning and precautions for use on Jarisch-Herxheimer reaction and to add Jarisch-Herxheimer reaction as an undesirable effect with an unknown frequency.

Summary of recommendation(s)

- The MAHs for doxycycline-containing medicinal products should submit to EMA or to the national competent authorities of the MSs as applicable, within 60 days, a variation for amending the product information[16].

For the full PRAC recommendation, see EMA/PRAC/610975/2017 published on 23/10/2017 on the EMA website.

4.3.6. Flucloxacillin (NAP)

Applicant(s): various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Signal of high anion gap metabolic acidosis (HAGMA)

EPITT 18844 – Follow-up to April 2017

Background

For background information, see PRAC minutes April 2017.

The MAH replied to the request for information on the signal of HAGMA and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of high anion gap metabolic acidosis (HAGMA) when flucloxacillin is used concomitantly with paracetamol, the PRAC agreed that the product information of flucloxacillin-containing medicinal products should be amended to include a special warning and precautions for use concerning concomitant administration of flucloxacillin and paracetamol, as well as to add information on the interaction between flucloxacillin and paracetamol. In addition, MAHs should be requested to add HAGMA as an undesirable effect reported in very rare cases in post marketing settings, when flucloxacillin is used concomitantly with paracetamol.

Summary of recommendation(s)

- The MAHs for flucloxacillin-containing products should submit to EMA or to the national competent authorities of the MSs as applicable, within 60 days, a variation for amending the product information[17].

For the full PRAC recommendation, see EMA/PRAC/610975/2017 published on 23/10/2017 on the EMA website.

[16] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly
[17] Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is to be updated accordingly

4.3.7. Gefitinib - IRESSA (CAP) - EMEA/H/C/001016/SDA/024

Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of recall phenomenon

EPITT 18857 – Follow-up to April 2017

Background

For background information, see PRAC minutes April 2017.

The MAH replied to the request for information on the signal of recall phenomenon and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from the cumulative review provided by the MAH for Iressa (gefitinib), the PRAC agreed that the current evidence does not warrant any regulatory action at this stage.

Summary of recommendation(s)

- The MAH for Iressa (gefinitib) should closely monitor reports of recall phenomenon, radiation recall pneumonitis and potentiation of radiation injuries in PSURs.

4.3.8. Insulin[18]: insulin aspart – NOVOMIX (CAP) - EMEA/H/C/000308/SDA/054, NOVORAPID (CAP)- EMEA/H/C/000258/SDA/047; insulin bovine (NAP); insulin degludec – TRESIBA (CAP) - EMEA/H/C/002498/SDA/011; insulin degludec, insulin aspart – RYZODEG (CAP) - EMEA/H/C/002499/SDA/006, insulin degludec, liraglutide – XULTOPHY (CAP) - EMEA/H/C/002647/SDA/003; insulin detemir – LEVEMIR (CAP) - EMEA/H/C/000528/SDA/052; insulin glargine – ABASAGLAR (CAP) - EMEA/H/C/002835/SDA/004, LANTUS (CAP) - EMEA/H/C/000284/SDA/053, LUSDUNA (CAP) - EMEA/H/C/004101/SDA/002, TOUJEO (CAP) - EMEA/H/C/000309/SDA/052; insulin glulisine – APIDRA (CAP) - EMEA/H/C/000557/SDA/041; insulin human (rDNA) – ACTRAPHANE (CAP) - EMEA/H/C/000427/SDA/024, ACTRAPID (CAP) - EMEA/H/C/000424/SDA/025, INSULATARD (CAP), INSULIN HUMAN WINTHROP (CAP) - EMEA/H/C/000761/SDA/008, INSUMAN (CAP) - EMEA/H/C/000201/SDA/048, MIXTARD (CAP) - EMEA/H/C/000428/SDA/026, PROTAPHANE (CAP) - EMEA/H/C/000442/SDA/028; insulin human, insulin isophane (NAP); insulin lispro – HUMALOG (CAP) - EMEA/H/C/000088/SDA/031, LIPROLOG (CAP) - EMEA/H/C/000393/SDA/024; insulin porcine (NAP)

Applicant(s): Eli Lilly Regional Operations GmbH (Abasaglar); Eli Lilly Nederland B.V. (Humalog, Liprolog); Novo Nordisk A/S (Actraphane, Actrapid, Insulatard, Levemir, Mixtard, NovoMix, NovoRapid, Protaphane, Ryzodeg, Tresiba, Xultophy); Merck Sharp & Dohme Limited (Lusduna); Sanofi-aventis Deutschland GmbH (Apidra, Lantus, Toujeo, Insulin Human Winthrop, Insuman); various

PRAC Rapporteur: Julie Williams

Scope: Signal of potential increased risk of medication error associated with withdrawing

[18] Pre-filled pens and cartridges

insulin from pre-filled pens and cartridges, leading to dysglycaemia

EPITT 18893 – Follow-up to May 2017

Background

For background information, see PRAC minutes May 2017.

The MAHs replied to the request for information on the signal of potential increased risk of medication error associated with withdrawing insulin from pre-filled pens and cartridges, leading to dysglycaemia. The responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, including the data submitted by the MAHs (Sanofi, Eli Lilly and Novo Nordisk), the PRAC agreed that the views of healthcare professional (HCP) experts and patients on medication errors and diabetes should be sought to better inform PRAC when considering measures to reduce the risk of medication errors associated with extracting insulin from pre-filled pens or from the cartridges intended for use with reusable pens.

Summary of recommendation(s)

- The PRAC adopted a list of questions (LoQ) for the consultation with HCP experts and patients. Following their input, the PRAC will issue a further recommendation.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

5.1.1. Betrixaban - EMEA/H/C/004309

Scope: Treatment of prophylaxis of venous thromboembolism (VTE)

5.1.2. Brigatinib - EMEA/H/C/004248

Scope: Treatment of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC)

5.1.3. Burosumab - EMEA/H/C/004275, Orphan

Applicant: Kyowa Kirin Limited

Scope: Treatment of X-linked hypophosphataemia (XLH)

5.1.4. Emicizumab - EMEA/H/C/004406

Scope, accelerated assessment: Treatment and routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors

5.1.5. Enclomifene - EMEA/H/C/004198

Scope: Treatment of hypogonadotrophic hypogonadism

5.1.6. Hydrocortisone - EMEA/H/C/004416, PUMA[20]

Scope: Treatment of adrenal insufficiency

5.1.7. Insulin glargine - EMEA/H/C/004280

Scope: Treatment of diabetes mellitus

5.1.8. Masitinib - EMEA/H/C/004398, Orphan

Applicant: AB Science

Scope: Treatment of amyotrophic lateral sclerosis

5.1.9. Peramivir - EMEA/H/C/004299

Scope: Treatment of influenza

5.2. Medicines in the post-authorisation phase – PRAC-led procedures

See Annex I 15.2.

5.3. Medicines in the post-authorisation phase – CHMP-led procedures

See Annex I 15.3.

6. Periodic safety update reports (PSURs)

6.1. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only

See also Annex I 16.1.

6.1.1. Alemtuzumab - LEMTRADA (CAP) - PSUSA/00010055/201703

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

Background

[20] Paediatric-use marketing authorisation(s)

Alemtuzumab is a recombinant immunoglobulin (Ig) G1 kappa monoclonal antibody indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lemtrada, a centrally authorised medicine containing alemtuzumab, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Lemtrada (alemtuzumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a new contraindication for patients with severe active infection in order to delay treatment with alemtuzumab until resolution of the infection. In addition, the product information should be updated to amend the existing warning on listeriosis/listeria meningitis to further minimise the risk of infection and to include a warning on pneumonitis in order to advise patients to report symptoms of infection to a physician. In addition, listeria meningitis should be added as an undesirable effect with an unknown frequency as well as pneumonitis with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should discuss whether it would be relevant to perform a review of tumefactive demyelinating lesions (TDL) in patients receiving alemtuzumab for B-cell chronic lymphocytic leukaemia (B-CLL). In addition, the MAH should perform cumulative reviews of pulmonary alveolar haemorrhage in relation to alemtuzumab treatment and to hepatobiliary disorders. Finally, considering the number of cases of listeriosis, the MAH should discuss whether the current additional risk minimisation measures are sufficient and whether a further update is required.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.2. Collagenase clostridium histolyticum[22] - XIAPEX (CAP) - PSUSA/00000871/201702

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Collagenase clostridium histolyticum is a proteinase indicated, as a centrally authorised medicine, for the treatment of Dupuytren's contracture in adult patients with a palpable cord and for the treatment of Peyronie's disease with a palpable plaque and a curvature deformity of at least 30 degrees at the start of therapy.

[21] Update of SmPC sections 4.3, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[22] Treatment of Dupuytren's contracture and treatment of Peyronie's disease only

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xiapex, a centrally authorised medicine containing collagenase clostridium histolyticum, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Xiapex (collagenase clostridium histolyticum) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'cold intolerance of the treated fingers' as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should provide further details on the cases reported with arthrodesis and finger amputation. In addition, the MAH should comment on the two cases with spontaneous abortion or spontaneous miscarriage reported in the treatment of edematous fibrosclerotic panniculopathy and provide information on a possible dose relationship of collagenase clostridium histolyticum with regard to this issue. Finally, the MAH should discuss the need to update the product information regarding consideration of extending the time to first sexual intercourse/sexual activity after the last injection.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.3. Dexmedetomidine - DEXDOR (CAP) - PSUSA/00000998/201703 (with RMP)

Applicant: Orion Corporation

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Dexmedetomidine is an alpha-2 adrenoceptor agonist indicated for the sedation of adult intensive care unit (ICU) patients requiring a sedation level not deeper than arousal in response to verbal stimulation.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Dexdor, a centrally authorised medicine containing dexmedetomidine, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Dexdor (dexmedetomidine) in the approved indication remains unchanged.
- Nevertheless, the product information should be updated to include polyuria as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[24].

[23] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- In the next PSUR, the MAH should submit a cumulative review of cases of oliguria.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.4. Eluxadoline - TRUBERZI (CAP) - PSUSA/00010528/201703

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Eluxadoline is a locally acting, mixed mu opioid receptor (μOR) agonist and delta opioid receptor (δOR) antagonist as well as a kappa opioid receptor (κOR) agonist. It is indicated in adults for the treatment of irritable bowel syndrome with diarrhoea (IBS-D).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Truberzi, a centrally authorised medicine containing eluxadoline, and issued a recommendation on its marketing authorisation(s). For further background, see PRAC minutes September 2017.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Truberzi (eluxadoline) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a recommendation that a physician experienced in diagnosis and management of gastrointestinal disorders should initiate and supervise treatment. Furthermore, the contraindication section is updated to include a list of conditions that predispose to the obstruction of the biliary tree and/or pancreatic duct. Furthermore, a warning on the increased risk of pancreatitis with or without sphincter of Oddi spasm in patients taking eluxadoline should be added to ensure that patients are informed and monitored for signs and symptoms suggestive of pancreatitis and to instruct them to stop treatment with eluxadoline and seek medical attention in the event of such symptoms. Finally, patients should be instructed not to use alcohol while on treatment with eluxadoline. Therefore the current terms of the marketing authorisation(s) should be varied[25].
- The MAH should inform healthcare professionals of these changes via a direct healthcare professional communication (DHPC). The PRAC reviewed and agreed with the content of the DHPC and the communication plan for further agreement by CHMP.
- In the next PSUR, the MAH should include a critical assessment of cases of pancreatitis, as well as re-evaluate whether the contraindications in the product information can be considered effective risk minimisation measures.

[24] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[25] Update of SmPC sections 4.2, 4.3 and 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.5. Fingolimod - GILENYA (CAP) - PSUSA/00001393/201702

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated for single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) in adults under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Gilenya, a centrally authorised medicine containing fingolimod, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Gilenya (fingolimod) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a contraindication for patients with underlying cardiac conditions[26]. In addition, a warning on immunosuppressive effects should be added to ensure that physicians carefully monitor patients especially those with concurrent conditions or known factors such as previous immunosuppressive therapy. If this risk is suspected, physicians should consider discontinuation on a case-by-case basis. Furthermore, the existing warning on infections should be amended in order to ensure that patients are referred to physicians experienced in treating infections. The existing warning on cutaneous neoplasms should be also further refined to ensure that patients treated with fingolimod are instructed to exercise caution and to avoid exposure to sunlight without protection and should not receive concomitant phototherapy with ultraviolet B (UV-B)-radiation or psoralen plus ultraviolet A (PUVA)-photochemotherapy. Moreover, squamous cell carcinoma should be added as an undesirable effect with a rare frequency, as well as Merkel cell carcinoma with an unknown frequency. Finally, the frequency of the undesirable effect Kaposi's sarcoma should be updated from unknown to very rare. As a consequence, the current terms of the marketing authorisation(s) should be varied[27].
- The MAH should inform healthcare professionals of these changes via a direct healthcare professional communication (DHPC). The PRAC reviewed and agreed with the content of the DHPC and the communication plan for further agreement by CHMP.

[26] Patients with myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure in the previous 6 months, patients with severe cardiac arrhythmias requiring anti-arrhythmic treatment with class Ia and class III anti-arrhythmic drugs, patients with second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not wear a pacemaker as well as patients with a baseline QTc interval ≥ 500 msec

[27] Update of SmPC sections 4.3, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- In the next PSUR, the MAH should discuss adequate risk minimisation measures including a revision of the educational material taking into account the duration of treatment with fingolimod in light of opportunistic infections and the risk of cancer. With regard to pregnancy and reproduction toxicity cases, the MAH should provide a detailed review of cases with congenital anomalies and analyse the potential pattern of malformations with a separate analysis according to the timing of exposure during pregnancy. In addition, the MAH should investigate the reasons for pregnancies where hormonal contraception has been used and propose an update of the product information and adequate additional measures to minimise the risk of fingolimod exposure during pregnancy, if considered necessary. Moreover, the MAH should carefully review the current risk minimisation measures for healthcare professionals and patients and propose to update the RMP and educational materials with particular regard to off label use, blood count and liver transaminases checks.
- The MAH should submit to EMA, within 60 days, a detailed review of cases of T cell-lymphoma including a discussion on the potential dechallenge effect as well as a review on the risk of relapses with tumefactive lesions and the need to inform prescribers. The MAH should propose to update the product information as applicable.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.6. Ibritumomab tiuxetan - ZEVALIN (CAP) - PSUSA/00001704/201702

Applicant: Spectrum Pharmaceuticals B.V.

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

Background

Ibritumomab tiuxetan is a recombinant murine immunoglobin (Ig) G1 kappa monoclonal antibody indicated as consolidation therapy after remission induction with rituximab in previously untreated patients with follicular lymphoma and for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zevalin, a centrally authorised medicine containing ibritumomab tiuxetan, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Zevalin (ibritumomab tiuxetan) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to clarify existing information related to the undesirable effect of myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML) and state the indication in which the undesirable effect was observed. Therefore the current terms of the marketing authorisation(s) should be varied[28].

[28] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- The MAH should submit to EMA, within 90 days, further information relating to median time to develop MDS/AML as well as on whether the risk of MDS/AML increases or decreases over time. In addition, the MAH should evaluate the type of multiple cytogenetic abnormalities at individual patient level in order to identify whether specific abnormalities are present in relation to treatment with Zevalin. Furthermore, the MAH should comment on the number of patients who, in addition to complex cytogenetics, have cytogenetic abnormalities normally associated with poor prognostic groups or therapy-related MDS/AML. Finally, the MAH should provide a detailed review on whether these patient characteristics differ between treatment and control groups and assess any implications on the benefit/risk balance of Zevalin.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.7. Ixekizumab - TALTZ (CAP) - PSUSA/00010493/201703

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Ixekizumab is an immunoglobulin (Ig) G4 monoclonal antibody, interleukin inhibitor indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Taltz, a centrally authorised medicine containing ixekizumab, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Taltz (ixekizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include anaphylaxis as an undesirable effect with a rare frequency and to modify the existing hypersensitivity warning to add the term anaphylaxis. Therefore the current terms of the marketing authorisation(s) should be varied[29].
- In the next PSUR, the MAH should provide a detailed discussion on the potential pathological mechanism of exacerbation and *de novo* development of inflammatory bowel disease (IBD) associated with ixekizumab as well as a discussion on the need for additional risk minimisation measures as applicable. Furthermore, the MAH should present a review of cases of suicidal ideation and behaviour.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

[29] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.8. Nalmefene - SELINCRO (CAP) - PSUSA/00010120/201702

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Nalmefene is an opioid system modulator indicated for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level (DRL), without physical withdrawal symptoms and who do not require immediate detoxification.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Selincro, a centrally authorised medicine containing nalmefene, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Selincro (nalmefene) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning to alert healthcare professionals that the risk of suicidal ideation in alcohol and substance abusers, with or without accompanying depression, is not reduced by nalmefene treatment. In addition, the product information should be updated to include myalgia as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[30].
- In the next PSUR, the MAH should provide a detailed review of the latest available data on suicidality and associated events. In addition, the MAH should provide cumulative reviews of cases of skin eruptions and related events and of cases reporting priapism and erectile dysfunction. The MAH should discuss the need to update the product information and make proposals as appropriate.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.9. Naloxegol - MOVENTIG (CAP) - PSUSA/00010317/201703

Applicant: Kyowa Kirin Limited

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Naloxegol is a peripheral opioid receptor antagonist indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s).

[30] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Moventig, a centrally authorised medicine containing naloxegol, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Moventig (naloxegol) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hypersensitivity as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[31].
- In the next PSUR, the MAH should provide a cumulative review of cases of rectal haemorrhage. In addition, the MAH should provide a review on whether there is evidence of use outside the label recommendations in reported cases of gastrointestinal (GI) perforation and a discussion on the need to consider further risk minimisation measures in this context.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.10. Naltrexone, bupropion - MYSIMBA (CAP) - PSUSA/00010366/201703

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Naltrexone is a mu-opioid antagonist and bupropion is an inhibitor of neuronal dopamine and norepinephrine reuptake. The combination of naltrexone/bupropion is indicated as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Mysimba, a centrally authorised medicine containing naltrexone/bupropion, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Mysimba (naltrexone/bupropion) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include angioedema as an undesirable effect with a very rare frequency for the combination product, as currently it is only included for monocomponent-products. Therefore the current terms of the marketing authorisation(s) should be varied[32].

[31] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[32] Update of SmPC section 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.11. Pembrolizumab - KEYTRUDA (CAP) - PSUSA/00010403/201703

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Pembrolizumab is a monoclonal antibody binding to the programmed cell death-1 (PD-1) receptor and blocking its interaction with ligands PD-L1 and PD-L2. Pembrolizumab is indicated for the treatment of advanced unresectable or metastatic melanoma, of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) and of relapsed or refractory classical Hodgkin's lymphoma (cHL) and for the treatment of locally advanced or metastatic urothelial carcinoma in adults under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Keytruda, a centrally authorised medicine containing pembrolizumab, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Keytruda (pembrolizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include pneumonia as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[33].
- In the next PSUR, the MAH should provide reviews on the incidence of cardiac arrhythmia and of pericarditis across the different randomised controlled clinical trials and include pooled analyses of these data. The MAH should discuss the need to update the product information accordingly. In addition, the MAH should provide cumulative reviews of organising pneumonitis, hepatitis reactivation and pure red cell aplasia or erythroblastopenia. Finally, the MAH should provide reviews of use in patients with pre-existing autoimmune diseases, as well as of de novo myasthenia gravis, Lambert-Eaton syndrome and myasthenia gravis exacerbation. The MAH should discuss the need to update the product information as applicable. Where necessary, any other risk minimisation measures should be proposed.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

[33] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.12. Rotigotine - LEGANTO (CAP); NEUPRO (CAP) - PSUSA/00002667/201702

Applicant: UCB Manufacturing Ireland Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Rotigotine is a dopamine agonist indicated for the symptomatic treatment of moderate to severe idiopathic restless legs syndrome (RLS) in adults and for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy or in combination with levodopa.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Leganto and Neupro, centrally authorised medicines containing rotigotine, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Leganto and Neupro (rotigotine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include diarrhoea as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[34].
- In the next PSUR, the MAH should provide reviews of cases of memory impairment and of dementia.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.13. Ruxolitinib - JAKAVI (CAP) - PSUSA/00010015/201702

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Ruxolitinib is a protein kinase inhibitor indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (MF)[35], post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis as well as for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Jakavi, a centrally authorised medicine containing ruxolitinib, and issued a recommendation on its marketing authorisation(s).

[34] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[35] Also known as chronic idiopathic myelofibrosis

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Jakavi (ruxolitinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to extend the existing warning on tuberculosis to polycythaemia vera patients and to include pneumonia as an undesirable effect with a common frequency in MF patients. Therefore the current terms of the marketing authorisation(s) should be varied[36].
- In the next PSUR, the MAH should provide cumulative reviews of cases of hypersensitivity reactions as well as of peripheral neuropathy. The MAH should discuss the need to update the product information and/or the RMP accordingly.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.14. Ulipristal acetate[37] - ESMYA (CAP) - PSUSA/00009325/201702

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Ulipristal acetate is a selective progesterone receptor modulator indicated, as Esmya, for the treatment of moderate to severe symptoms of uterine fibroids.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Esmya, a centrally authorised medicine containing ulipristal acetate, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Esmya (ulipristal acetate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include drug hypersensitivity and angioedema as undesirable effects with an uncommon and an unknown frequency respectively. Therefore the current terms of the marketing authorisation(s) should be varied[38].
- The MAH should submit to EMA, within 60 days, a cumulative review of the important potential risk 'drug induced liver injury' and discuss the need to update the product information and/or the RMP accordingly.
- In the next PSUR, the MAH should closely monitor cases of severe/serious hypersensitivity.

[36] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[37] Treatment of moderate to severe symptoms of uterine fibroids only
[38] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.2. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)

See Annex I 16.2.

6.3. PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only

See also Annex I 16.3.

6.3.1. Amlodipine (NAP) - PSUSA/00000174/201703

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Amlodipine is a calcium ion influx inhibitor indicated for first line treatment of hypertension and myocardial ischaemia, whether due to fixed obstruction such as stable angina, and/or to vasospasm/vasoconstriction such as Prinzmetal's or variant angina of the coronary vasculature. Amlodipine is also indicated to reduce the risk of fatal coronary heart disease, non-fatal myocardial infarction, stroke, coronary revascularisation, and hospitalisation due to angina in patients with coronary artery disease.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing amlodipine, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of amlodipine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on drug interaction between amlodipine and known inducers of CYP3A4[39], to advise healthcare professionals to monitor blood pressure and to consider dose regulation both during and after concomitant medication particularly with strong CYP3A4 inducers. In addition, the warning on the risk of amlodipine excretion in breast milk should be amended to mention that amlodipine is excreted in human milk and the effect of amlodipine on infants is unknown in light of the current knowledge. Finally, the product information is updated to add toxic epidermal necrolysis (TEN) as an undesirable effect with an

[39] Cytochrome P450 3A4

unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[40].

The frequency of PSUR submission should be revised from yearly to five-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.3.2. Bilastine (NAP) - PSUSA/00003163/201703

Applicant(s): various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

Background

Bilastine is a H1-receptor antagonist indicated for the symptomatic treatment of allergic rhino-conjunctivitis and urticaria.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing bilastine, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of bilastine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include hypersensitivity reactions as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[41].
- In the next PSUR, the MAH should provide cumulative reviews of case reports of extrasystoles and of vomiting, and discuss the need to update the product information as applicable. In addition, the MAH should provide a detailed review of cases where exposure to bilastine during pregnancy is reported as well as a cumulative analysis relating to the safety profile in the elderly.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.3.3. Ethinylestradiol, gestodene[42] (NAP) - PSUSA/00010145/201702

Applicant(s): various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

[40] Update of SmPC sections 4.5, 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[41] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[42] Transdermal application only

Background

Ethinylestradiol is an estrogen and gestodene is a progestogen. In combination, ethinylestradiol/gestodene is indicated as a transdermal patch for female hormonal contraception.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing ethinylestradiol/gestodene, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ethinylestradiol/gestodene-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'skin reactions such as erythema, pruritus and skin irritation outside the application site' as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[43].
- In the next PSUR, the MAH(s) should provide a cumulative analysis of cases of application site discolouration and a cumulative review of cases of menorrhagia. MAH(s) should also discuss the need to update the product information as applicable.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.3.4. Flubendazole (NAP) - PSUSA/00001400/201702

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Flubendazole is an anti-helminthic indicated for the treatment of single or mixed infestations by *Enterobius vermicularis* (pinworm), *Trichuris trichiura* (whipworm), *Ascaris lumbricoides* (large roundworm), *Ancylostoma duodenale* and *Necator americanus* (hookworm).

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing flubendazole, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of flubendazole-containing medicinal products in the approved indications remains unchanged.

[43] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- Nevertheless, the product information should be updated regarding the safety of flubendazole use during pregnancy in light of the reviewed data, taking into account that abnormalities or foetal malformation cases have also been reported for other benzimidazole antihelmintic products which are contraindicated in pregnancy. Therefore, flubendazole is not recommended during pregnancy or in women of childbearing potential not using contraception. As a consequence, the current terms of the marketing authorisation(s) should be varied[44].
- In the next PSUR, the MAH(s) should re-categorise the safety concern 'use during pregnancy and lactation' from missing information to an important potential risk. The MAH(s) should also strictly monitor any cases of exposure to flubendazole during pregnancy.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.3.5. Haemophilus type b conjugate vaccines (NAP) - PSUSA/00001584/201702

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

Haemophilus type b conjugate vaccine is a bacterial vaccine indicated for the prevention of *Haemophilus influenzae* type b (Hib) and invasive infections such as meningitis, septicaemia, cellulitis, arthritis, epiglottitis, pneumopathy and osteomyelitis.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised haemophilus type b conjugate vaccines, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of haemophilus type b conjugate vaccines in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include rash generalised as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[45].

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

[44] Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[45] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.3.6. Ipratropium, salbutamol (NAP) - PSUSA/00001781/201701

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

Background

Ipratropium is an anticholinergic bronchodilator and salbutamol is a β2-agonist agent. In combination, ipratropium/salbutamol is indicated in adults, adolescents and children above 12 years for the management of bronchospasm in patients suffering from chronic obstructive pulmonary disease (COPD) who require regular treatment with both ipratropium bromide and salbutamol.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing ipratropium/salbutamol, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ipratropium/salbutamol-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on lactic acidosis as an increase in lactate levels may lead to dyspnoea and compensatory hyperventilation which could be misinterpreted as a sign of asthma treatment failure. Therefore, patients should be monitored for the development of elevated serum lactate and consequent metabolic acidosis in this setting. Furthermore, lactic acidosis has been also reported in association with high therapeutic doses as well as overdoses of short-acting beta-agonist therapy. Therefore monitoring for elevated serum lactate and consequent metabolic abnormalities may be indicated in the setting of overdose. Finally, lactic acidosis should be added to the product information as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[46].

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.3.7. Loratadine (NAP) - PSUSA/00001907/201702

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

[46] Update of SmPC sections 4.4, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Loratadine is a tricyclic antihistamine indicated for the relief of symptoms associated with perennial and/or seasonal allergic rhinitis and allergic skin disorders.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing loratadine, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of loratadine-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, MAH(s) should present a cumulative review of cases of interaction with simvastatin and other statins leading to myopathies.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.3.8. Omega-3-acid-ethyl esters (NAP) - PSUSA/00010312/201701

Applicant(s): various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Omega-3-acid-ethyl esters are ethyl esters of polyunsaturated fatty acids (PUFA) indicated for the treatment of hypertriglyceridaemia and as secondary prevention in patients with previous myocardial infarction (MI).

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing omega-3-acid-ethyl esters, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of omega-3-acid-ethyl esters-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the risk of hypersensitivity reactions in patients allergic to fish and to include the undesirable effects pruritus and urticaria with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[47].
- In the next PSUR, the MAHs should provide cumulative reviews of cases of off-label use associated with serious adverse effects. In addition, MAHs should monitor and discuss cases of epistaxis, of hyperglycaemia and of toxic skin eruption. The MAHs should

[47] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

propose to update the product information as applicable. Moreover, MAHs should provide clinical evidence related to increase in bleeding time in patients with haemorrhagic diathesis or receiving treatment with anticoagulants or other drugs that act on the coagulation system. MAHs should critically assess available evidence to characterise this risk.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.3.9. Saccharomyces boulardii (NAP) - PSUSA/00009284/201702

Applicant(s): various

PRAC Lead: Eva Jirsova

Scope: Evaluation of a PSUSA procedure

Background

Saccharomyces boulardii is a replacement for intestinal flora indicated for adjuvant symptomatic treatment of diarrhoea in addition to rehydration and/or dietetic measures as well as for prophylaxis and treatment of antibiotic-associated diarrhoea and recurrence of *Clostridium difficile* disease (CDD) in addition to vancomycin and metronidazole.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing *Saccharomyces boulardii*, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of *Saccharomyces boulardii*-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to contraindicate the use of *Saccharomyces boulardii* in critically ill or immunocompromised patients due to the risk of fungaemia and to add a warning on fungaemia to ensure that special attention is paid to the handling of *Saccharomyces boulardii* medicinal product(s) in the presence of patients mainly with central venous catheters but also with peripheral catheters, in order to avoid any contamination by touch and/or the spread of microorganisms by air. In addition, the product information should be updated to include fungaemia in critically ill or immunocompromised patients as an undesirable effect with a very rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[48].
- The MAH should inform healthcare professionals of these changes via a direct healthcare professional communication (DHPC). The PRAC reviewed and agreed with the content of the DHPC and the communication plan.
- In the next PSUR, the MAH(s) should closely monitor adverse effects associated with off-label use of *Saccharomyces boulardii* and provide a detailed assessment. In addition, the MAHs should provide a discussion on the relevant cases and scientific data concerning

[48] Update of SmPC sections 4.2, 4.3, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

the risk of enteral translocation of ingested microorganisms and subsequent fungaemia in patients with damaged intestinal mucosa.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[49]

See also Annex I 17.1.

7.1.1. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/PSA/S/0016.1

Applicant(s): Celgene Europe Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of an amended protocol for study CC-5013-MDS-012: a post-authorisation, non-interventional, retrospective, drug-utilisation study to describe the pattern of use of lenalidomide in patients with myelodysplastic syndromes (MDS) as agreed in the conclusions of EMEA/H/C/PSA/S/0016 in April 2017

Background

Revlimid is a centrally authorised medicine containing lenalidomide. It is indicated for the treatment of adult patients with previously untreated multiple myeloma under certain conditions, as well as indicated in combination for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. In addition, Revlimid is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. Revlimid is also indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

In April 2014, the PRAC adopted the protocol for a non-interventional PASS (study CC-5013-MDS-012) designed as a retrospective drug-utilisation study (DUS) to describe patterns of Revlimid use. The MAH submitted a substantial protocol amendment (protocol amendment 1, version 3.0) further to the feasibility results, to revise various timelines and introduce major changes including the specification of data sources, reduction of the sample size and modification of the study secondary objectives to which the PRAC objected in March 2017 raising four concerns. In July 2017, the MAH submitted a revised proposal for an amended

[49] In accordance with Article 107n of Directive 2001/83/EC

PASS protocol (version 4.0). For further background, see PRAC minutes April 2014 and PRAC minutes March 2017.

Endorsement/refusal of the protocol

- The PRAC, having considered the amended protocol version 4.0, in accordance with Article 107n of Directive 2001/83/EC, concluded that the study protocol could be acceptable provided that the MAH amends it based on the identified outstanding issues. In particular, the MAH should include in safety analyses (secondary objective) both on-/off-label patients already included in the DUS (primary objective). In addition, the MAH should compare the risks studied in terms of hazard ratios as done in study CC-5013-MDS-004[50] as well as planning adjustment strategies in multivariate analyses (secondary objective) taking into account baseline characteristics collected for the primary objective.
- The MAH should submit a revised PASS protocol within 30 days to the EMA. A 30 days-assessment timetable will be applied.

7.1.2. Levonorgestrel (NAP) - EMEA/H/N/PSA/S/0020.1

Applicant(s): Bayer Pharma AG (Jaydess, Luadei); various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Amendment to the previously agreed protocol (version 2.2) for EURAS-LCS12 study: a European active surveillance study of LCS-12 (levonorgestrel intrauterine contraceptive system releasing 12 mcg levonorgestrel/24h in vitro), an intra-uterine device (IUD) for Jaydess and Luadei (levonorgestrel) to investigate whether LCS-12 is associated with an increased risk of unintended pregnancy compared to Mirena and to copper IUDs (previous conclusions of procedure EMEA/H/N/PSA/j/0006.1 adopted by PRAC in September 2016) as per the request for supplementary information (RSI) agreed in the conclusions of procedure EMEA/H/N/PSA/S/0020 in July 2017

Background

Levonorgestrel is a progestogen indicated, via an intrauterine device, for contraception and the treatment of menorrhagia.

The EURAS-LCS12 study is part of the post approval imposed commitment SE/H/1186/01 to further investigate whether there are differences in unintended pregnancy rates with LSC12 (levonorgestrel intrauterine contraceptive system releasing 12 mcg levonorgestrel/24h in vitro) compared to Mirena (levonorgestrel-releasing intrauterine system) or copper intra-uterine device (IUD). The initial PASS protocol was endorsed by PRAC on 10 April 2014. A third amendment to the PASS protocol aimed at implementing the advice given by the independent Safety Monitoring and Advisory Council to modify the pre-set recruitment rules between IUD groups was submitted by the MAH and objected by the PRAC in July 2017. The MAH submitted responses to the list of questions endorsed in July 2017. For further background, see PRAC minutes July 2017.

Endorsement/refusal of the protocol

[50] A multicentre, randomized, double-blind, placebo-controlled, 3-arm study of the efficacy and safety of 2 doses of lenalidomide versus placebo in red blood cell (RBC) transfusion-dependent subjects with low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion (Del) 5q[31] cytogenetic abnormality

- The PRAC, having considered the amended protocol version 2.3 in accordance with Article 107n of Directive 2001/83/EC together with the MAH's responses to the list of outstanding issues endorsed by the Committee in July 2017, objected to the proposed amended protocol for the above listed medicinal product(s), as the Committee considered that that the design of the study did not fulfil the study objectives and that the conduct of the study, with the proposed amendment, will promote the use of the medicinal product.
- The PRAC recommended that the proposed capping of the control arms should be removed as the study might become promotional but the proposed extended recruitment period should be kept. A proposal for the evaluation of the signal concerning neuropsychiatric reactions in the ongoing PASS study should be included and consideration should be given to expanding the recruiting network by introducing additional countries where the product is marketed, e.g. Denmark.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 days-assessment timetable will be applied.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[51]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[52]

7.3.1. Hydroxyethyl starch (NAP) - EMEA/H/N/PSR/S/0009

Applicant(s): Fresenius Kabi Deutschland GmbH (Volulyte, Voluven; various)

PRAC Rapporteur: Qun-Ying Yue

Scope: Results of a retrospective drug utilisation study (DUS) to investigate the routine use of hydroxyethyl starch (HES)-containing infusion solutions in hospital settings

Background

Hydroxyethyl starch (HES) products derive from potato or corn with different molecular weights and substitution ratios (e.g. 200/0.5; 130/0.4). They are approved for intravenous use for infusion and are indicated for treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient. In line with the conclusions from 2013 of referral procedures under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1348) and Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1376) for HES-containing medicines, MAHs were required as a condition to the marketing authorisations (Annex IV) to conduct a drug utilisation study (DUS) in several Member States in order to evaluate the effectiveness of the agreed risk minimisation measures. The study protocol was to be submitted within 6 months after the European Commission decision dated 19 December 2013, and the final study report within 24 months after the protocol agreement. In July 2015, the PRAC endorsed the PASS (drug utilisation study) protocol version 1.4 submitted by the MAH Fresenius Kabi Deutschland GmbH. For further background, see PRAC minutes October 2013,

[51] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004
[52] In accordance with Article 107p-q of Directive 2001/83/EC

PRAC minutes July 2014, PRAC minutes October 2014, PRAC minutes February 2015 and PRAC minutes July 2015.

The final study report was submitted to EMA by MAH Fresenius Kabi Deutschland GmbH on 5 July 2017. The PRAC discussed the final study results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'retrospective drug utilisation study to investigate the routine use of hydroxyethyl starch (HES)-containing infusion solutions in hospitals', the PRAC considered that supplementary information was required before a recommendation could be made on the risk-benefit balance of medicinal products containing the active substance poly (o-2-hydroxyethyl) starch concerned by the PASS final report.
- The MAH should provide sales data and patient exposure data stratified per year and per EU member state before and after the implementation of the measures of the referral concluded in 2013 (EMEA/H/A-107i/1376) to get an estimation of the absolute number of patients being exposed and provide a context for the PASS results.
- The MAH should submit responses to the request for supplementary information within 7 days to EMA. A 30 days-assessment timetable will be applied.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[53]

See also Annex I 17.4.

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation

See also Annex I 17.5.

7.5.1. Valproate (NAP) - EMEA/H/N/PSI/J/0002

Applicant(s): Sanofi-aventis Recherche & Development (on behalf of a consortium)

PRAC Rapporteur: Sabine Straus

Scope: Second interim results report for a joint drug utilisation study (DUS) of valproate and related substances conducted in Europe aiming at describing the prescribing practices before and after the dissemination of risk minimisation measures (RMM) (i.e. educational materials and direct healthcare professional communication (DHPC)) and assessing the effectiveness of these measures using databases, as requested in the outcome of the referral procedure on valproate and related substances (EMEA/H/A-31/1387) concluded in 2014

Background

Valproic acid is an acidic organic compound, and valproate and related salts and esters are indicated for the treatment of generalised, partial or other types of epilepsy, and for the

[53] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

treatment of manic episodes in bipolar disorder under certain conditions. Valproate is also indicated in some Member States to prevent migraine headaches.

In October 2014, the PRAC adopted a recommendation for consideration by the CMDh for the referral procedure conducted under Article 31 of Directive 2001/83/EC (EMA/612389/2014) for valproate and related substances strengthening the restrictions on the use of valproate in female patients. In addition, to improve the safety information and awareness of both female patients and healthcare professionals (HCPs) about the risks of valproate exposure during pregnancy, the PRAC recommended providing educational materials (EM) to HCPs. As part of the risk minimisation measures (RMMs), the PRAC requested the MAHs of valproate-containing products to perform also a drug utilisation study (DUS) to assess the effectiveness of the measures and to further characterise the prescribing patterns for valproate with a pre- and post-implementation analysis and assessment, in more than one Member State. For further background, see PRAC minutes January 2016, PRAC minutes July 2015 and PRAC minutes September 2015.

A revised protocol for this DUS was submitted to the PRAC by a consortium of MAHs in accordance with the conditions to the marketing authorisations included in the EC decision Annex IV for the referral under Article 31 of Directive 2001/83/EC (EMA/612389/2014) for valproate-containing medicine and was endorsed by the PRAC in January 2016 (see PRAC minutes January 2016).

The consortium of MAHs submitted a first interim report that was assessed by PRAC in April 2017 (for further background, see PRAC minutes April 2017). At the current meeting, PRAC discussed the outcome of the assessment of the second interim report of this PASS.

Summary of advice

- Based on the PRAC Rapporteur's review, the PRAC considered that the second interim report of the DUS concerning valproate-containing products is subject to a request for supplementary information, before a recommendation can be made.
- For all pregnancies identified in the DUS including valproate exposed and unexposed, the consortium of MAHs is requested to provide a more in-depth overview of information regarding the outcome of the pregnancies.
- The consortium of MAHs should submit responses to the request for supplementary information (RSI) within 30 days to EMA. A 30 day assessment timetable will be applied. This recommendation is without prejudice to the final conclusions of the ongoing referral procedure under Article 31 of Directive 2001/83/EC for valproate-containing medicinal products (EMEA/H/A-31/1454) (see under 3.2.3.).

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

7.8. Ongoing Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

7.9. Final Scientific Advice (Reports and Scientific Advice letters)

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

8. Renewals of the marketing authorisation, conditional renewal and annual reassessments

8.1. Annual reassessments of the marketing authorisation

None

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

Disclosure of information on results of pharmacovigilance inspections could undermine the protection of the purpose of these inspections, investigations and audits. Therefore such information is not reported in the minutes.

9.3. Others

None

10. Other safety issues for discussion requested by the CHMP or the EMA

10.1. Safety related variations of the marketing authorisation

None

10.2. Timing and message content in relation to Member States' safety announcements

None

10.3. Other requests

None

10.4. Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

11. Other safety issues for discussion requested by the Member States

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC Brexit ancillary working group

PRAC lead: Almath Spooner

At the organisational matters teleconference on 12 October 2017, the chair of the PRAC ancillary working group on Brexit preparedness reported to PRAC from the fourth group meeting that took place on 18 September 2017 as well from the cross-Committee EMA 'Working Group on Committees' operational preparedness for human medicines' meeting

held on 4 October 2017.

12.1.2. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of qualitative goals

PRAC lead: Martin Huber, Menno van der Elst, Tatiana Magalova, Albert van der Zeijden, Jan Neuhauser, Ulla Wändel Liminga

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016), the PRAC was updated at the organisational matters teleconference held on 12 October 2017 which was run 9 months after the implementation of the BPG recommendations (qualitative measures) collected from June 2016. Building on the survey outcome as well as on the quantitative measures collected for the third 2017 quarter of PRAC meetings, the need for further improvements was discussed.

12.1.3. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals

PRAC lead: Martin Huber, Menno van der Elst, Tatiana Magalova, Albert van der Zeijden, Jan Neuhauser, Ulla Wändel Liminga

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016), the PRAC was updated at the organisational matters teleconference held on 12 October 2017 on quantitative measures collected for the third 2017 quarter of PRAC meetings. For previous update, see PRAC minutes July 2017.

12.2. Coordination with EMA Scientific Committees or CMDh

12.2.1. Guideline on safety and efficacy follow-up – risk management plan of advanced therapy medicinal products (ATMP) – update

PRAC lead: Brigitte Keller-Stanislawski, Dolores Montero Corominas, Sabine Straus, Ulla Wändel Liminga, Julie Williams

As a follow-up to the last PRAC discussions on the exercise to revise the 'Guideline on safety and efficacy follow-up – risk management plan of advanced therapy medicinal products (ATMPs)' (EMEA/149995/2008) (see PRAC minutes January 2016 and PRAC minutes April 2016 , PRAC minutes July 2016 , PRAC minutes February 2017 and PRAC minutes April 2017), the PRAC further discussed the handling of the updated version of the guideline and reinforced that the principles of GVP module V on 'risk management system' should be followed. Follow-up discussion is scheduled at the November 2017 PRAC meeting (scheduled on 23-26 October 2017).

12.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

None

12.4. Cooperation within the EU regulatory network

12.4.1. PRAC strategic review and learning meeting, Estonia, 16-18 October 2017

PRAC lead: Maia Uusküla

The PRAC was presented with a consolidated agenda for the PRAC strategic review and learning meeting (SRLM), including a joint session between CHMP-PRAC, to be held on 16-18 October 2017, under the Estonian presidency of the Council of the EU.

12.4.2. Reflection paper on the use of extrapolation in the development of medicines for paediatrics

Further to the discussion in September 2017 (see PRAC minutes September 2017) on the updated reflection paper on the 'use of extrapolation in the development of medicines for paediatrics', including the last comments received and the outcome of the 'Workshop on extrapolation of efficacy and safety in medicine development across age group' dated 17-18 May 2016 (EMA/478467/2016), the PRAC adopted the reflection paper for public consultation.

Post-meeting: following further adoption at the PDCO and CHMP, the reflection paper (EMA/199678/2016) was published on 13 October 2017 on the EMA website for public consultation until 14 January 2018.

12.5. Cooperation with International Regulators

None

12.6. Contacts of the PRAC with external parties and interaction with the Interested Parties to the Committee

None

12.7. PRAC work plan

12.7.1. PRAC work plan 2018 – preparation

PRAC lead: June Raine

At the organisational matters teleconference held on 12 October 2017, the EMA Secretariat presented the initiation of the PRAC work plan for 2018 taking into account the activities completed, progress made as well as priorities identified at the level of the Committee, EMA, HMA and EU network. A draft work plan will be due for discussion at the November 2017 PRAC meeting (scheduled on 23-26 October 2017).

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system

None

12.8.2. Marketing authorisation applications (MAA) expected for 2017 – Q3 2017 update

The EMA Secretariat presented, at the organisational matters teleconference held on 12 October 2017, for information a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline'). For previous update, see PRAC minutes July 2017.

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections – template for sharing assessor's information

The EMA Secretariat presented to PRAC a draft template for sharing of information from assessors to inspectors on pharmacovigilance matters developed by the Pharmacovigilance Inspectors Working Group (PhV IWG)-PRAC subgroup. The PRAC noted that it is a separate template for sharing of information from the template from inspectors to assessors recently finalised by the PhV IWG in July 2017. PRAC delegates were invited to provide written comments on the draft template from assessors to inspectors by 20 October 2017. As next steps, the template will be further consolidated by the PhV IWG-PRAC subgroup and a pilot phase will be initiated.

12.9.3. Pharmacovigilance audits - Pharmacovigilance Audit Facilitation Group (PAFG)

PRAC lead: Caitriona Fisher (PAFG chair)

The Pharmacovigilance Audit Facilitation Group (PAFG) was organised within the Heads of Medicines Agencies (HMA) Working Group of Quality Managers (WGQM) in order to foster a common approach to pharmacovigilance audits. For further background, see PRAC minutes May 2013, PRAC minutes January 2014, PRAC minutes March 2014, PRAC minutes April 2014, PRAC minutes September 2014, and PRAC minutes February 2015.

Having achieved the goal of providing guidance, document templates, and practical training to Competent Authorities, the PAFG work plan was delivered. National Competent Authorities have now gained experience in internal audits of pharmacovigilance for at least the last five to six years, and have reported on the third two-year cycle of audits to the European Commission under the Pharmacovigilance Directive. Besides updating the checklists as good pharmacovigilance practice (GVP) modules are revised, there is no outstanding work item for the PAFG.

It was discussed how PRAC's responsibilities on pharmacovigilance audit as outlined in Article 61a (6) of Regulation (EC) No 726/2004 would be affected by PAFG dismantlement and if such responsibilities could be transferred to another group.

In conclusion, the PRAC endorsed that the PAFG had fulfilled its objectives and agreed that the PAFG chair will discuss the handover of current responsibilities of PAFG to the WGQM and report to PRAC on a regular basis[54].

12.10. Periodic safety update reports (PSURs) & Union reference date (EURD) list

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

The PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list, and noted the progress made.

12.10.3. PSURs repository

None

12.10.4. Roadmap for periodic safety update reports (PSUR) activities update: report from joint assessor-industry training, 22 September 2017

PRAC lead: Menno van der Elst, Ulla Wändel Liminga

At the organisational matters teleconference held on 12 October 2017, the EMA Secretariat reported to the PRAC on the joint industry/assessor webinar training[55] held at EMA on 22 September 2017 in the context of the PSUR roadmap activities and following the publication of the explanatory note to the GVP module VII on PSUR (EMA/102307/2017) and the Q&A on PSUSA: guidance document for assessors (EMA/518909/2016). PRAC noted that this had been a valuable training. Further update is scheduled at the November 2017 PRAC meeting[56].

12.10.5. Union reference date list – consultation on the draft list

The PRAC endorsed the draft revised EURD list version September 2017 reflecting the PRAC's comments impacting on the data lock points (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC minutes April 2013).

[54] Ideally biannually
[55] Training video recording
[56] Scheduled on 23-26 October 2017

Post-meeting note: following the PRAC meeting of October 2017, the updated EURD list was adopted by the CHMP and CMDh at their October 2017 meetings and published on the EMA website on 17/10/2017, see:

Home> Human Regulatory>Pharmacovigilance>Periodic safety update reports>EURD list> List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)

12.11. Signal management

12.11.1. Good pharmacovigilance practice (GVP) module IX on Signal management – revision 1 and addendum

PRAC lead: Sabine Straus

The PRAC adopted revision 1 of GVP module IX on 'signal management' and addendum I on 'methodological aspects of signal detection from spontaneous reports of suspected adverse reactions' following the public consultation held at the end of 2016 (for further background before public consultation, see PRAC minutes April 2016), the PRAC discussion on the handling of MAHs' signals after the go-live of the new EudraVigilance (EV) system in November 2017 (see PRAC minutes May 2017), the further aspects discussed at PRAC in July 2017 (see PRAC minutes July 2017) and the subsequent review by EMA Secretariat and the European Commission (EC).

Post-meeting note: On 12 October 2017, GVP module IX revision 1 and GVP module IX - Addendum I were published on the EMA website and come into force on 22 November 2017.

12.11.2. Signal management – feedback from Signal Management Review Technical (SMART) Working Group

PRAC lead: Sabine Straus

The SMART Working Group (SMART WG) work stream WS1 originally scheduled on 25 September 2017 was cancelled.

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

12.12.3. List of products under additional monitoring – consultation on the draft list

The PRAC was informed of the updates made to the list of products under additional monitoring.

Post-meeting note: The updated additional monitoring list was published on 25/10/2017 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring).

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

12.14.2. Tools, educational materials and effectiveness measurement of risk minimisations

None

12.14.3. Good pharmacovigilance practice (GVP) module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' – revision 3

PRAC lead: Sabine Straus, Torbjörn Callréus

At the organisational matters teleconference held on 12 October 2017, the EMA Secretariat presented to PRAC a proposal to revise[57] GVP module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' to highlight the main topics warranting high priority for further guidance/clarifications. Since the publication in April 2014 of GVP module XVI revision 1, there have been a number of activities in the area of risk minimisation design, implementation, and evaluation that have further evolved. These activities supported the identification of gaps and opportunities for which further regulatory guidance is needed. The PRAC endorsed the proposal to update GVP module XVI and further discussion will be scheduled in due course in 2018.

12.15. Post-authorisation safety studies (PASS)

12.15.1. Good pharmacovigilance practices (GVP) module VIII on 'Post-authorisation safety studies (PASS)' – revision 3 in line with update of GVP module VI on 'Management and reporting of adverse reactions to medicinal products'

The EMA Secretariat presented to PRAC a minor revision made to GVP module VIII on 'Post-authorisation safety studies (PASS)' to align some wording with revision 2 of GVP module VI

[57] As revision 3

on 'Collection, management and submission of reports of suspected adverse reactions to medicinal products'. The PRAC adopted revision 3 of GVP module VIII.

Post-meeting note: On 12 October 2017, GVP module VIII revision 3 was published on the EMA website and comes into force on 13 October 2017.

12.15.2. Post-authorisation Safety Studies – non-imposed PASS

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Good pharmacovigilance practice (GVP) module XV on 'Safety communication' – revision 1

PRAC lead: Amelia Cupelli, Sabine Straus

As a follow-up to last month's discussion (see PRAC minutes September 2017), the PRAC adopted revision 1 of GVP module XV on 'safety communication'.

Post-meeting note: On 12 October 2017, GVP module XV revision 1 was published on the EMA website and comes into force on 13 October 2017.

12.18.2. Public participation in pharmacovigilance

None

12.18.3. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Guideline on good pharmacovigilance practices (GVP) Annex I on 'Definitions' - revision 4

The EMA Secretariat presented to PRAC revision 4 of GVP Annex I on 'Definitions' including an update of several definitions, with all recent legal and GVP developments having already been otherwise approved by PRAC. The PRAC endorsed the revised document.

Post-meeting note: On 12 October 2017, GVP Annex I revision 4 was published on the EMA website and comes into force on 13 October 2017.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[58]

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[59].

14.1.1. Baricitinib – OLUMIANT (CAP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Signal of pneumonia

EPITT 18950 – New signal

Lead Member State: UK

14.1.2. Exenatide – BYDUREON (CAP), BYETTA (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of cardiac arrhythmias

[58] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

[59] Either MA(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

EPITT 18938 – New signal

Lead Member State: SE

14.1.3. Iloprost – VENTAVIS (CAP)

Applicant: Bayer Pharma AG

PRAC Rapporteur: Caroline Laborde

Scope: Signal of bradycardia

EPITT 18935 – New signal

Lead Member State: FR

14.1.4. Teriflunomide – AUBAGIO (CAP)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Signal of lymphoma

EPITT 18960 – New signal

Lead Member State: DE

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

None

15.2. Medicines in the post-authorisation phase – PRAC-led procedure

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the variation procedure for the below mentioned medicine(s).

15.2.1. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/WS1164/0033; Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/WS1164/0008; Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/WS1164/0030

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of the RMPs (Jardiance (version 12.1), Glyxambi (version 3.0), Synjardy (version 9.2)) to reflect changes requested in the PRAC recommendation for the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442). In addition, the RMPs are updated to include

pancreatitis as an important potential risk for empagliflozin-containing medicines following the PRAC recommendation for the PSUSA procedure for canagliflozin-containing products (PSUSA/00010077/201603) adopted in October 2016

15.2.2. Miglustat - ZAVESCA (CAP) - EMEA/H/C/000435/II/0057, Orphan

Applicant: Actelion Registration Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of the RMP (version 12.2) in order to remove important identified risks such as diarrhoea and other gastrointestinal (GI) events and tremor as well as important potential risks such as seizure in Niemann-Pick type C (NP-C) patients

15.2.3. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[60]) - EMEA/H/W/002300/II/0020

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of the RMP (version 3.0) in order to 1) add cerebral malaria as an important potential risk; 2) add mortality by gender as missing information; 3) add the WHO[61] pilot implementation programme as a category 3 study; 4) change the study dates for studies malaria-073 (200596, phase IIIb randomized, open, controlled study to evaluate the immunogenicity and safety of Mosquirix, when administered as primary vaccination at 6, 7.5 and 9 months of age with or without coadministration of measles and rubella and yellow fever vaccines to children living in sub-Saharan, Africa), EPI-MAL-002 (115055, an observational cohort study to estimate the incidence of adverse event of special interest (AESI), of meningitis and of other adverse events (AE) leading to hospitalisation or death, in children, prior to implementation of Mosquirix), EPI-MAL-003 (115056, a prospective surveillance study to evaluate the safety, the effectiveness and the impact of Mosquirix in infants and young children in sub-Saharan Africa), EPI-MAL-005 (116682, an epidemiology study to assess *Plasmodium falciparum* parasite prevalence and malaria control measures in catchment areas of two interventional studies pre- and post-Mosquirix introduction (EPI-MAL-002 and EPI-MAL-003) to assess, in field conditions, vaccine benefit-risk in children in sub-Saharan Africa), EPI-MAL-010 (205071, a longitudinal, cross-sectional ancillary study of the EPI-MAL-005 study to evaluate the genetic diversity in circumsporozoite sequences before and after the implementation of Mosquirix in malaria-positive subjects ranging from 6 months to less than 5 years of age); 5) amend the protocol of study EPI-MAL-002; 6) update the draft protocol of study EPI-MAL-003; 7) provide a new draft of the protocol of study EPI-MAL-010, 8) provide a new protocol for the pilot implementation programme

15.2.4. Turoctocog alfa - NOVOEIGHT (CAP) - EMEA/H/C/002719/II/0020

Applicant: Novo Nordisk A/S

[60] Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)
[61] World Health Organization

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of the RMP (version 3) and submission of an amended protocol for PASS study NN7008-3553 (a multicentre non-interventional study of safety and efficacy of turoctocog alfa (rFVIII) during long-term treatment of severe and moderately severe haemophilia A (FVIII =<2%), a category 3 study in the RMP) to update the milestone timelines in order to integrate the required additional pharmacovigilance activities, which include a change in the last patient last visit (LPLV) date and a change in the clinical trial report (CTR) finalisation date. In addition, the duration of the trial has been amended from 4 to 7 years

15.3. Medicines in the post-authorisation phase – CHMP-led procedure

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the updated versions of the RMP for the below mentioned medicine(s).

15.3.1. Abiraterone acetate - ZYTIGA (CAP) - EMEA/H/C/002321/II/0047

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer and in combination with androgen deprivation therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 14.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

15.3.2. Alectinib - ALECENSA (CAP) - EMEA/H/C/004164/II/0001

Applicant: Roche Registration Limited

PRAC Rapporteur: Patrick Batty

Scope: Extension of indication to first line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). As a consequence, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 2.0) are updated accordingly

15.3.3. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0017

Applicant: Celgene Europe Limited

PRAC Rapporteur: Eva Segovia

Scope: Update of section 4.4 of the SmPC to include a warning on serious diarrhoea, nausea, and vomiting following a safety cumulative review of all data sources. The Package Leaflet is updated accordingly. In addition, the RMP (version 9.0) is updated to classify serious diarrhoea, nausea, and vomiting as important potential risks. The MAH took the opportunity to introduce editorial changes in Annex IIIA and to bring the Product Information in line with the latest QRD template (version 10.0)

15.3.4. Atazanavir,cobicistat - EVOTAZ (CAP) - EMEA/H/C/003904/WS1193/0018; Atazanavir, atazanavir sulfate - REYATAZ (CAP) - EMEA/H/C/000494/WS1193/0113

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Caroline Laborde

Scope: Update of sections 4.3 and 4.5 of the SmPC to include information on the contraindicated co-administration with grazoprevir-containing products, including elbasvir/grazoprevir fixed dose combination used for the treatment of chronic hepatitis C infection following the results of interaction studies. The Package Leaflets and the RMPs (Evotaz (version 5.0), Reyataz (version 13.0)) are updated accordingly. In addition, the MAH took the opportunity to make some editorial changes and typographical corrections in the Reyataz and Evotaz Product Information

15.3.5. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0018, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include children aged one month and older to the authorised population for the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated in order to include the new population, update the posology and the safety information. The Package Leaflet and the RMP (version 6.0) are updated accordingly

15.3.6. Brivaracetam - BRIVIACT (CAP) - EMEA/H/C/003898/II/0010/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped application consisting of 1) extension of indication to include adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy 4 years of age and older. As a consequence, sections 4.1, 4.2, 4.7, 5.1 and 5.2 of the SmPC are updated; 2) submission of a 5ml oral syringe and adaptor for the paediatric population. The Package Leaflet, Labelling and the RMP (version 6.1) are updated accordingly. The submission also includes a final environmental risk assessment (ERA) for the inclusion of the paediatric population in accordance with the new proposed indication

15.3.7. Carfilzomib - KYPROLIS (CAP) - EMEA/H/C/003790/II/0017/G, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Grouped variation consisting of: 1) update of sections 4.8 and 5.1 of the SmPC in order to update the efficacy and safety information based on the second interim analysis of the overall survival data from study ENDEAVOR (study 20130398): a randomised, multicentre, open-label, phase 3 study of carfilzomib and dexamethasone compared to

bortezomib with dexamethasone in patients with relapse multiple myeloma. The Package Leaflet and the RMP (version 9.0) are updated accordingly; 2) update of section 4.8 of the SmPC in order to revise the frequencies of certain adverse drug reactions based on the pooled data set including ENDEAVOR and seven recently completed studies. In addition, the MAH took the opportunity to add editorial changes in sections 4.2, 4.4, 6.3 and 6.6 of the SmPC. Several editorial changes are also included in the package leaflet and labelling

15.3.8. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/II/0015

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.4, 4.5, 4.8 and 5.2 of the SmPC in order to update the safety information based on the primary pharmacokinetic (PK) and preliminary safety results of food effect study CLDK378A2112: a multicentre, randomized open label study to assess the systemic exposure, efficacy, and safety of 450 mg ceritinib taken with a low-fat meal and 600 mg ceritinib taken with a low-fat meal as compared with that of 750 mg ceritinib taken in the fasted state in adult patients with anaplastic lymphoma kinase (ALK) rearranged (ALK-positive) metastatic non-small cell lung cancer (NSCLC). The Package Leaflet and the RMP (version 9.0) are updated accordingly

15.3.9. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/II/0050

Applicant: Pfizer Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Update of sections 4.2, 4.3, 4.4, 4.8 and 5.2 of the SmPC in order to update the information about hepatic impairment based on the results of study A8081012: a phase 1 study evaluating the effect of hepatic impairment on the pharmacokinetics and safety of crizotinib in advanced cancer patients. The package leaflet and the RMP (version 7.4) are updated accordingly. The final study report of study A8081012 is included

15.3.10. Daptomycin - CUBICIN (CAP) - EMEA/H/C/000637/II/0061

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to extend the *S. aureus* bacteraemia indication to include paediatric patients 1 to 17 years of age. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet, Labelling and the RMP (version 10.0) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 10) and to combine the SmPCs for both strengths (350 and 500 mg)

15.3.11. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/II/0026, Orphan

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the frequencies of adverse reactions included in the tabulated list of adverse reactions and to update the clinical efficacy and safety information based on the results from study 2006-05 (listed as category 3 in the RMP): a phase 3, open-label expanded access study designed to provide access to defibrotide as an investigational new drug to patients with severe hepatic veno-occlusive disease. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to bring the SmPC in line with the latest QRD template (version 10), to update the list of local representatives in the package leaflet and to correct a translation error in the Polish, Finnish, Danish and Latvian versions

15.3.12. Denosumab - XGEVA (CAP) - EMEA/H/C/002173/II/0056

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to modify the special warnings and precautions for use and undesirable effects sections following the performance of a cumulative safety review of multiple vertebral fractures (MVF) following treatment discontinuation based on two clinical trials: study 20060359: an ongoing randomized, placebo-controlled, blinded study of denosumab as adjuvant treatment for women with early-stage breast cancer at high risk of recurrence and study 20040113: a completed phase 2 study comparing denosumab and intravenous (IV) bisphosphonate treatment, collected data on bone turnover markers during the 32-week post-treatment follow-up period as well as based on post-marketing experience data. The Package Leaflet and the RMP (version 26.0) are updated accordingly. A direct healthcare professional communication (DHPC) is also proposed to inform prescribers about the new identified risk of MVF following discontinuation of Xgeva

15.3.13. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0036/G

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Grouped variation consisting of: 1) submission of a clinical study report (CSR) for study 109HV321: a randomized, double-blind, phase 3b study to evaluate the safety and tolerability of BG00012 (dimethyl fumarate) when administered as 240 mg BID (twice daily) dose regimen with and without aspirin compared to placebo or following a slow titration (category 3); 2) submission of a CSR for study 109MS406 (ASSURE): a phase 4, randomized, double-blind study with a safety extension period to evaluate the effect of aspirin on flushing events in subjects with relapsing-remitting multiple sclerosis treated with Tecfidera (dimethyl fumarate) delayed-release capsules (category 4). The RMP (version 9.0) is updated accordingly

15.3.14. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0037

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Submission of a clinical study report (CSR) for study 109MS307: an open-label study

to assess the immune response to vaccination in Tecfidera-treated versus interferon-treated subjects with relapsing forms of multiple sclerosis (category 3). As a consequence, section 4.5 of the SmPC is updated. The Package Leaflet and the RMP (version 9.0) are updated accordingly

15.3.15. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/WS1190/0210/G; LIFMIOR (CAP) - EMEA/H/C/004167/WS1190/0009/G

Applicant: Pfizer Limited

PRAC Rapporteur: Patrick Batty

Scope: Grouped worksharing quality variation. An addendum to the RMP (version 6.3) is submitted accordingly

15.3.16. Human normal immunoglobulin - HIZENTRA (CAP) - EMEA/H/C/002127/II/0087

Applicant: CSL Behring GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include immunomodulatory therapy for the treatment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy to prevent relapse of neuromuscular disability and impairment. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 4.0) are updated accordingly

15.3.17. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0033/G, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Grouped variations consisting of: 1) update of sections 4.4 and 5.1 of the SmPC in order to update the safety information related to bleeding related events based on final results from study PCYC-1132-NT (RMP, category 3 (MEA 004.1) study): an in-vitro study to evaluate the effect of ibrutinib on platelet aggregation. The Package Leaflet is updated accordingly; 2) update of section 4.4 and 4.5 of the SmPC in order to update the safety information based on the final results from study LYM1003 (RMP, category 3 (MEA 009.1) study): a drug-drug interaction study to assess steady state pharmacokinetic (PK) of repeated oral doses of ibrutinib alone in patients with B-cell malignancies and when combined with a moderate and strong CYP3A[62] inhibitor. The Package Leaflet is updated accordingly; 3) update of section 4.5 of the SmPC in order to update the safety information based on the final results from study FK12024: a drug-drug interaction (DDI) study with CYP3A inhibitor posaconazole in simulated subjects. The Package Leaflet is updated accordingly; 4) update of section 4.4 of the SmPC in order to update the safety information on antimicrobial prophylaxis following routine pharmacovigilance activity; 5) update of the RMP in order to extend the closure date of study PCYC-1112-CA (ANX 003.2: a randomized, multicentre, open-label, phase 3 study of the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib (PCI-32765) versus ofatumumab in patients with relapsed or refractory chronic

[62] Cytochrome P450, family 3, subfamily A

lymphocytic leukaemia/small lymphocytic lymphoma) to Q2 2019. Next yearly update will be submitted in Q2 2018. Annex II has been updated accordingly; 6) update of the RMP to include an additional action for study PCI-32765 CAN3001 (MEA017) to provide a 'further interim report in 5 years' from the time of the cut-off date of the current report (12 November 2015)' as agreed in the CHMP outcome for procedure EMA/H/C/003791/MEA 017. The RMP (version 6.8) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

15.3.18. Idelalisib – ZYDELIG (CAP) – EMEA/H/C/003843/II/0035/G

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Patrick Batty

Scope: Update of section 5.3 of the SmPC in order to revise the carcinogenicity information for idelalisib based on final results from two long term carcinogenicity studies (TX-312-2017, TX-312-2019). The RMP version 2.3 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.0.

15.3.19. Insulin degludec - TRESIBA (CAP) - EMEA/H/C/002498/II/0028

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 5.1 of the SmPC based on new clinical data from a cardiovascular outcome trial EX1250-4080 (DEVOTE): a randomised, double-blind and event-driven clinical study with a median duration of 2 years comparing the cardiovascular safety of Tresiba (insulin degludec) versus insulin glargine (100 units/mL) in patients with type 2 diabetes mellitus (T2DM) at high risk of cardiovascular events. The RMP (version 8) is updated accordingly

15.3.20. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/II/0008, Orphan

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the clinical study report (CSR) for study E7080-J081-208: a phase 2 multicentre, open-label, single-arm study to evaluate the safety of once daily oral administration of lenvatinib (E7080) in subjects with advanced thyroid cancer

15.3.21. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/II/0017

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to reflect the long-term safety and efficacy data from study VX12 809 105: a phase 3, rollover study to evaluate the safety and efficacy of long term treatment with lumacaftor/ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous or heterozygous for the F508del cystic fibrosis

transmembrane conductance regulator (CFTR) mutation (MEA 001). The RMP (version 2.7) is updated accordingly. In addition, the MAH took the opportunity to bring the Product Information in line with the latest QRD template (version 10)

15.3.22. Migalastat - GALAFOLD (CAP) - EMEA/H/C/004059/II/0011, Orphan

Applicant: Amicus Therapeutics UK Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 4.2 of the SmPC to provide further information on missing doses and to improve the wording on the administration of migalastat with food. No new data is submitted to support these changes. In addition, the MAH took this opportunity to include the ATC[63] code and to update the local representatives in the package leaflet. As a consequence, changes are introduced in Annexes I, IIIA and IIIB. The RMP (version 2.0) is updated accordingly

15.3.23. Nitric oxide - INOMAX (CAP) - EMEA/H/C/000337/II/0051

Applicant: Linde Healthcare AB

PRAC Rapporteur: Julie Williams

Scope: Quality variation to introduce an additional container closure system. The RMP (version 6.0) is updated to reflect post-authorisation experience with the new cylinder closure system

15.3.24. Pegaspargase - ONCASPAR (CAP) - EMEA/H/C/003789/X/0008

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Patrick Batty

Scope: Line extension application to add a new pharmaceutical form, powder for solution for injection/infusion (750 U/mL). The RMP (version 2.0) is updated accordingly

15.3.25. Peginterferon alfa-2a - PEGASYS (CAP) - EMEA/H/C/000395/II/0091

Applicant: Roche Registration Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Extension of indication to include paediatric patients from 3 to less than 18 years of age with chronic hepatitis B in the immune-active phase for Pegasys. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add efficacy and safety information from study YV25718: a phase 3b parallel group, open label study of pegylated interferon alfa-2a monotherapy compared to untreated control in children with HBeAg positive chronic hepatitis B. The Package Leaflet and the RMP (version 8.0) are updated accordingly

[63] Anatomical therapeutic chemical

15.3.26. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0039/G, Orphan

Applicant: Incyte Biosciences UK Ltd

PRAC Rapporteur: Patrick Batty

Scope: Grouped variations consisting of the submission of the final reports from two nonclinical studies performed to investigate the potential mechanism of action of ponatinib leading to vascular occlusion, namely 1) study RPT-03346: evaluation of the effects of ponatinib on arterial remodeling and wall thickening in a murine model of stenosis; 2) study RPT-03342: investigation of the effects of ponatinib on photochemical-induced thrombosis in mice and rats, conducted to further explore the potential relationship between ponatinib and thrombosis in a photochemical induced thrombosis model in mice and rats. The RMP (version 18) is updated accordingly

15.3.27. Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/II/0019

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of section 4.8 of the SmPC of Sivextro concentrate for solution for infusion formulation in order to add information from study BAY119-2631/16121: a phase 3 randomized, double-blind, multicentre study comparing the efficacy and safety of intravenous to oral 6-day tedizolid phosphate and intravenous to oral 10 day linezolid for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and change the reported expected frequency of the adverse reaction 'infusion site phlebitis' from 'uncommon' to 'common'. The Package Leaflet is updated accordingly. The RMP (version 3.0) is also updated and includes a proposal to collect safety information regarding tedizolid phosphate by conducting three investigator initiated studies and deleting the original proposed long term safety study. The MAH also took the opportunity to make minor editorial corrections throughout the product information

15.3.28. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/II/0042/G

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variation consisting of the submission of the final reports for: 1) study MO25515 (MEA006): an open-label multicentre study to assess the safety of RO5185426 (vemurafenib) in patients with metastatic melanoma; 2) study GP28492 (ZeSS) (MEA010): a prospective observational safety study of patients with BRAFV600 mutation positive unresectable or metastatic melanoma treated with vemurafenib. The RMP (version 10.3) is updated accordingly

16. Annex I - Periodic safety update reports (PSURs)

Based on the assessment of the following PSURs, the PRAC concluded that the benefit-risk balance of the below mentioned medicines remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing

authorisation(s) together with the assessment report. As per agreed criteria, the procedures listed below were finalised at the PRAC level without further plenary discussion.

The next PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal, unless changes apply as stated in the outcome of the relevant PSUR/PSUSA procedure(s).

16.1. PSUR procedures including centrally authorised products only

16.1.1. Albiglutide - EPERZAN (CAP) - PSUSA/00010175/201703

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.2. Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) - ZALMOXIS (CAP) - PSUSA/00010530/201702

Applicant: MolMed SpA, ATMP[64]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.3. Anidulafungin - ECALTA (CAP) - PSUSA/00000215/201701

Applicant: Pfizer Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.4. Apremilast - OTEZLA (CAP) - PSUSA/00010338/201703

Applicant: Celgene Europe Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.5. Bedaquiline - SIRTURO (CAP) - PSUSA/00010074/201703

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

[64] Advanced therapy medicinal product

16.1.6. Belimumab - BENLYSTA (CAP) - PSUSA/00009075/201703

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.7. Betaine anhydrous[65] - CYSTADANE (CAP) - PSUSA/00000390/201702 (with RMP)

Applicant: Orphan Europe SARL

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.1.8. Bevacizumab - AVASTIN (CAP) - PSUSA/00000403/201702

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.9. Bosutinib - BOSULIF (CAP) - PSUSA/00010073/201703

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.10. Brentuximab vedotin - ADCETRIS (CAP) - PSUSA/00010039/201702

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.11. Ceftazidime, avibactam - ZAVICEFTA (CAP) - PSUSA/00010513/201702

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.1.12. Ceftolozane, tazobactam - ZERBAXA (CAP) - PSUSA/00010411/201703

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Adam Przybylkowski

[65] Centrally authorised product only

Scope: Evaluation of a PSUSA procedure

16.1.13. Cholic acid[66] - KOLBAM (CAP) - PSUSA/00010182/201703

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.14. Ciclosporin[67] - IKERVIS (CAP) - PSUSA/00010362/201703

Applicant: Santen Oy

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.15. Cobimetinib - COTELLIC (CAP) - PSUSA/00010450/201702

Applicant: Roche Registration Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.16. Dabigatran - PRADAXA (CAP) - PSUSA/00000918/201703

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

16.1.17. Dexamethasone[68] - NEOFORDEX (CAP) - PSUSA/00010480/201703

Applicant: Laboratoires CTRS

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.18. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), haemophilus type b conjugate vaccine (adsorbed) - VAXELIS (CAP) - PSUSA/00010469/201702

Applicant: MCM Vaccine B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

[66] Treatment of inborn errors in primary bile acid synthesis due to sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency or cholesterol 7α-hydroxylase (CYP7A1) deficiency indications only
[67] Topical use only
[68] Centrally authorised product indicated in symptomatic multiple myeloma only

Scope: Evaluation of a PSUSA procedure

16.1.19. Dulaglutide - TRULICITY (CAP) - PSUSA/00010311/201703

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.20. Eftrenonacog alfa - ALPROLIX (CAP) - PSUSA/00010499/201703

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.21. Eliglustat - CERDELGA (CAP) - PSUSA/00010351/201702

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.22. Emtricitabine, rilpivirine, tenofovir alafenamide - ODEFSEY (CAP) - PSUSA/00010514/201702

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.23. Enoxaparin[69] - INHIXA (CAP), THORINANE (CAP) - PSUSA/00010553/201703

Applicants: Pharmathen S.A. (Thorinane), Techdow Europe AB (Inhixa)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.24. Epoetin beta - NEORECORMON (CAP) - PSUSA/00001239/201702

Applicant: Roche Registration Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

[69] Biosimilars only

16.1.25. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/201702

Applicant: Chiesi Farmaceutici S.p.A., ATMP[70]

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.26. Fenofibrate, simvastatin - CHOLIB (CAP) - PSUSA/00010096/201702

Applicant: Mylan Products Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.27. Ferric maltol - FERACCRU (CAP) - PSUSA/00010476/201702

Applicant: Shield TX (UK) Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.28. Fluticasone propionate, salmeterol[71] - AERIVIO SPIROMAX (CAP), AIREXAR SPIROMAX (CAP) - PSUSA/00010531/201702

Applicant: Teva B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.29. Ganirelix - ORGALUTRAN (CAP) - PSUSA/00001517/201702

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.30. Glycopyrronium[72] - SIALANAR (CAP) - PSUSA/00010529/201703

Applicant: Proveca Limited

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

[70] Advanced therapy medicinal product
[71] Centrally authorised products only
[72] Centrally authorised product indicated for the treatment of severe sialorrhea only

16.1.31. Guanfacine - INTUNIV (CAP) - PSUSA/00010413/201703

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.32. Human alfa 1-proteinase inhibitor[73] - RESPREEZA (CAP) - PSUSA/00010410/201702

Applicant: CSL Behring GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.33. Human coagulation factor X - COAGADEX (CAP) - PSUSA/00010481/201703

Applicant: Bio Products Laboratory Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.34. Influenza vaccine (split virion, inactivated)[74] - IDFLU (CAP); INTANZA (CAP) - PSUSA/00001743/201703

Applicants: Sanofi Pasteur SA (IDflu), Sanofi Pasteur Europe (Intanza)

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.35. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) - OPTAFLU (CAP) - PSUSA/00001745/201703

Applicant: Seqirus GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.36. Isavuconazole - CRESEMBA (CAP) - PSUSA/00010426/201703

Applicant: Basilea Medical Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

[73] Centrally authorised product only
[74] Centrally authorised products only

16.1.37. Lapatinib - TYVERB (CAP) - PSUSA/00001829/201703

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.38. Nitisinone - ORFADIN (CAP) - PSUSA/00002169/201702

Applicant: Swedish Orphan Biovitrum International AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.39. Oritavancin - ORBACTIV (CAP) - PSUSA/00010368/201703

Applicant: The Medicines Company UK Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.40. Ospemifene - SENSHIO (CAP) - PSUSA/00010340/201702

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.41. Panobinostat - FARYDAK (CAP) - PSUSA/00010409/201702 (with RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.42. Pirfenidone - ESBRIET (CAP) - PSUSA/00002435/201702

Applicant: Roche Registration Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.43. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[75]) - EMEA/H/W/002300/PSUV/0022

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUR procedure

16.1.44. Prasugrel - EFIENT (CAP) - PSUSA/00002499/201702

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

16.1.45. Rasburicase - FASTURTEC (CAP) - PSUSA/00002613/201702

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.46. Reslizumab - CINQAERO (CAP) - PSUSA/00010523/201702

Applicant: Teva Pharmaceuticals Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.47. Safinamide - XADAGO (CAP) - PSUSA/00010356/201702

Applicant: Zambon S.p.A.

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.48. Sebelipase alfa - KANUMA (CAP) - PSUSA/00010422/201702

Applicant: Alexion Europe SAS

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

[75] Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

16.1.49. Teduglutide - REVESTIVE (CAP) - PSUSA/00009305/201702

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

16.1.50. Telavancin - VIBATIV (CAP) - PSUSA/00002879/201703

Applicant: Theravance Biopharma Ireland Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.51. Timolol, travoprost - DUOTRAV (CAP) - PSUSA/00002962/201702

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.52. Tobramycin (nebuliser solution)[76] - VANTOBRA (CAP) - PSUSA/00010370/201703

Applicant: Pari Pharma GmbH

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.53. Trastuzumab emtansine - KADCYLA (CAP) - PSUSA/00010136/201702 (with RMP)

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.2. PSUR procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)

16.2.1. Imiquimod - ALDARA (CAP); ZYCLARA (CAP); NAP - PSUSA/00001729/201701

Applicants: Meda AB (Aldara, Zyclara), various

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

[76] Centrally authorised product only

16.2.2. Voriconazole - VFEND (CAP); NAP - PSUSA/00003127/201702

Applicants: Pfizer Limited (Vfend), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3. PSUR procedures including nationally approved products (NAPs) only

16.3.1. Amisulpride (NAP) - PSUSA/00000167/201701

Applicant(s): various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.3.2. Amitriptyline hydrochloride, chlordiazepoxide (NAP) - PSUSA/00000171/201702

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.3. Beta-alanine (NAP) - PSUSA/00010510/201701

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.3.4. Carbomers (NAP) - PSUSA/00000557/201701

Applicant(s): various

PRAC Lead: Gabriela Jazbec

Scope: Evaluation of a PSUSA procedure

16.3.5. Cilostazol (NAP) - PSUSA/00010209/201702

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.6. Haemophilus type b and meningococcal group c conjugate vaccine (NAP) - PSUSA/00001583/201702

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.7. Human coagulation factor VIII[77] (NAP) - PSUSA/00009174/201702

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.8. Hydroxyethyl starch (NAP) - PSUSA/00001694/201703

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.9. Ipratropium (NAP) - PSUSA/00001780/201701

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.10. Levosalbutamol, salbutamol (NAP) - PSUSA/00010330/201701

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.11. Lisdexamfetamine (NAP) - PSUSA/00010289/201702

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.12. Loratadine, pseudoephedrine (NAP) - PSUSA/00001908/201702

Applicant(s): various

[77] Inhibitor bypassing fraction only

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.3.13. Moxonidine (NAP) - PSUSA/00002095/201701

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.14. Olodaterol (NAP) - PSUSA/00010245/201703

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.3.15. Oxatomide (NAP) - PSUSA/00002233/201701

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.16. Tick-borne encephalitis vaccine (inactivated) (NAP) - PSUSA/00002951/201701

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.17. Zanamivir (NAP) - PSUSA/00003141/201701

Applicant(s): various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Atazanavir, atazanavir sulfate - REYATAZ (CAP) - EMEA/H/C/000494/LEG 083.1

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Caroline Laborde

Scope: MAH's response to LEG 083 [comprehensive review of congenital anomalies reported with atazanavir, including a literature review and a discussion of the data gathered from the

antiretroviral pregnancy registry (APR)] as per the request for supplementary information (RSI) adopted at the October 2016 PRAC meeting

16.4.2. Desloratadine - AERIUS (CAP) - EMEA/H/C/000313/LEG 066

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Detailed review on movement disorders (including dystonia, tics and extrapyramidal symptoms) including a discussion on the need to update the product information with 'movement disorders' as applicable as requested in the conclusions of PSUSA/00000962/201607 adopted in March 2017

16.4.3. Desloratadine - AZOMYR (CAP) - EMEA/H/C/000310/LEG 066

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Detailed review on movement disorders (including dystonia, tics and extrapyramidal symptoms) including a discussion on the need to update the product information with 'movement disorders' as applicable as requested in the conclusions of PSUSA/00000962/201607 adopted in March 2017

16.4.4. Desloratadine - NEOCLARITYN (CAP) - EMEA/H/C/000314/LEG 066

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Detailed review on movement disorders (including dystonia, tics and extrapyramidal symptoms) including a discussion on the need to update the product information with 'movement disorders' as applicable as requested in the conclusions of PSUSA/00000962/201607 adopted in March 2017

16.4.5. Desloratadine, pseudoephedrine sulphate - AERINAZE (CAP) - EMEA/H/C/000772/LEG 015

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Detailed review on movement disorders (including dystonia, tics and extrapyramidal symptoms) including a discussion on the need to update the product information with 'movement disorders' as applicable as requested in the conclusions of PSUSA/00000962/201607 adopted in March 2017

16.4.6. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/LEG 156

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Detailed cumulative safety review of the safety concerns in the currently approved EU-RMP (i.e. important identified risks, important potential risks or missing information) that could be reclassified or deleted based on the available cumulative safety data, as requested in the conclusions of PSUSA/00010231/201608 adopted in April 2017

16.4.7. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/LEG 039.2

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's response to LEG 039 [cumulative review on cases of liver-related events (hepatotoxicity) as requested in the recommendation of PSUSA/00002653/201509 adopted by PRAC in April 2016] as per the request for supplementary information (RSI) adopted in March 2017

16.4.8. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/LEG 017.1

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 017 [detailed review on arterial and venous thromboembolic events (ATE/VTE) including a discussion on the biological plausibility based on the mechanism of action of ulipristal acetate, focusing on the role of oestrogen and progesterone as requested in the conclusions of PSUSA/00009325/201602 adopted by PRAC and CHMP in September 2016] as per the request for supplementary information (RSI) adopted in February 2017

16.4.9. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/LEG 035

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Review of cases of posterior reversible encephalopathy syndrome (PRES) as requested in the conclusions of PSUSA/00009329/201608 adopted in March 2017

16.4.10. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/LEG 036

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Review of cases of sarcoidosis as requested in the conclusions of PSUSA/00009329/201608 adopted in March 2017

16.4.11. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/LEG 037

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Cumulative review of cases of lymphopenia as requested in the conclusions of PSUSA/00009329/201608 adopted in March 2017

17. Annex I – Post-authorisation safety studies (PASS)

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, the PRAC adopted the conclusion of the Rapporteurs on their assessment for the medicines listed below without further plenary discussion.

17.1. Protocols of PASS imposed in the marketing authorisation(s)[78]

17.1.1. Ivabradine – CORLENTOR (CAP), IVABRADINE ANPHARM (CAP), PROCOROLAN (CAP) - EMEA/H/C/PSA/S/0022

Applicant(s): Les Laboratoires Servier (Corlentor, Procorolan), Anpharm Przedsiebiorstwo (Ivabradine Anpharm)

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for a drug utilisation study (DUS) in select European countries: a multinational, retrospective, observational study to assess effectiveness of risk-minimisation measures

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[79]

17.2.1. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/MEA 026.3

Applicant: Servier (Ireland) Industries Ltd.

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: MAH's response to MEA 026.2 [amendment to the protocol for cross sectional study CLE-20098-96-096: a non-interventional PASS: drug utilisation study (DUS) in selected European countries: a multinational, observational study to assess the effectiveness of risk-minimisation measures] as per the request for supplementary information (RSI) adopted in June 2017

17.2.2. Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/MEA 026.3

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: MAH's response to MEA 026.2 [amendment to the protocol for cross sectional study CLE-20098-96-096: a non-interventional PASS: drug utilisation study (DUS) in selected

[78] In accordance with Article 107n of Directive 2001/83/EC
[79] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

European countries: a multinational, observational study to assess the effectiveness of risk-minimisation measures] as per the request for supplementary information (RSI) adopted in June 2017

17.2.3. Cabozantinib – CABOMETYX (CAP) – EMEA/H/C/004163/MEA 001.1

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to MEA 001 [PASS protocol for study F-FR-60000-001: a non-interventional prospective study exploring the utilisation of cabozantinib in subjects with advanced renal cell carcinoma (RCC) following prior vascular endothelial growth factor (VEGF)-targeted therapy in real life settings in terms of dose modifications due to adverse events (AEs) when used as a second line therapy or third and later line therapy] as per the request for supplementary information (RSI) adopted in July 2017

17.2.4. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/MEA 045.2

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 045.1 [PASS protocol for study GS-EU-276-4027, a drug utilisation study (DUS) to characterize: 1) prescribers' level of knowledge about the key risks of Truvada for a pre-exposure prophylaxis (PrEP) indication and assess the effectiveness of risk minimisation measures; 2) prescribing practices in routine clinical practice of Truvada for PrEP by describing the demographics of human immunodeficiency virus (HIV)-1 uninfected individuals who were prescribed Truvada for PrEP, and the prescribed dosing schedule for Truvada for PrEP as reported by the prescriber, as a result of variation II/0126 finalised at CHMP/PRAC in July 2016 to extend the indication to PrEP] as per the request for supplementary information (RSI) adopted in May 2017

17.2.5. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/MEA 002

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Julie Williams

Scope: Protocol for a study/survey listed in the RMP as category 3 to measure the effectiveness of Suliqua educational materials set up to evaluate the knowledge and understanding of the key safety messages in the healthcare professional guide and the patient guide

17.2.6. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 004.3

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to MEA 004.2 [revised PASS protocol for study NB-452: a cross-

sectional survey to evaluate the effectiveness of the Mysimba physician prescribing checklist (PPC) among physicians in the EU] as per request for supplementary information (RSI) adopted in May 2017

17.2.7. Nusinersen - SPINRAZA (CAP) - EMEA/H/C/004312/MEA 002

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Synopsis for a protocol for a prospective longitudinal neuromuscular disease (NMD) registry in a research agreement with the Muscular Dystrophy Association (MDA) U.S: descriptive characteristics of individuals with spinal muscular atrophy (SMA)

17.2.8. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 002.1

Applicant: AbbVie Limited

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA-002 [registry protocol for a prospective observational study P16-562 to assess the long term safety profile of venetoclax in a Swedish cohort of chronic lymphocytic leukaemia (CLL) patients] as per the request for supplementary information (RSI) adopted in May 2017

17.3. Results of PASS imposed in the marketing authorisation(s)[80]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[81]

17.4.1. Aclidinium bromide - BRETARIS GENUAIR (CAP) - EMEA/H/C/002706/WS1207/0034; EKLIRA GENUAIR (CAP) - EMEA/H/C/002211/WS1207/0034

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report for study D6560R00005: a drug utilisation post-authorisation safety studies (DUS 1) in the United Kingdom, Denmark, and Germany listed as a category 3 study in the RMP (MEA002) aiming at describing the characteristics of new users of aclidinium bromide and of other chronic obstructive pulmonary disease (COPD) medications, evaluating the potential off-label use of aclidinium bromide in adults, pregnant women, and children, identifying and describing users of aclidinium bromide in patient subgroups for which there is missing information in the EU-RMP, and establishing a cohort of new users of aclidinium bromide for the future evaluation of safety concerns described in the RMP. The RMP (version 6.0) is updated accordingly

[80] In accordance with Article 107p-q of Directive 2001/83/EC
[81] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

17.4.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0062

Applicant: Genzyme Europe BV

PRAC Rapporteur: Caroline Laborde

Scope: Submission of the final study report for study ALGMYC08432: a non-interventional, non-imposed PASS entitled: 'Myozyme (alglucosidase alfa) safety information packet (SIP) effectiveness evaluation: a healthcare professional (HCP) survey' (Myozyme SIP EU HCP survey). The RMP (version 8.0) is updated accordingly

17.4.3. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0045

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report for study 109MS419 (listed as a category 3 study in the RMP): a retrospective, multicentre, observational study aimed to assess the effect of Tecfidera delayed-release capsules on lymphocyte subsets in patients with relapsing forms of multiple sclerosis

17.4.4. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/II/0054

Applicant: Hospira UK Limited

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final study report for a post-marketing surveillance study for Inflectra 100 mg (infliximab) to evaluate its safety and efficacy in Korea: study intended to identify any unexpected adverse events, serious adverse events and frequencies, pattern of occurrence of adverse events under the condition of general clinical practice as well as to determine any factor that may affect the safety and efficacy

17.4.5. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/II/0045

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final study report for a post-marketing surveillance study for Remsima 100 mg (infliximab) to evaluate its safety and efficacy in Korea: study intended to identify any unexpected adverse events, serious adverse events and frequencies, pattern of occurrence of adverse events under the condition of general clinical practice as well as to determine any factor that may affect the safety and efficacy

17.4.6. Human rotavirus, live attenuated - ROTARIX (CAP) - EMEA/H/C/000639/II/0100

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final report for study ROTA-085-PMS (115927) (listed as a category 3 study in the RMP): an observational prospective cohort study investigating the

incidence of intussusception after vaccination for rotavirus gastroenteritis, conducted to determine the incidence of intussusception after vaccination with Rotarix in Japan. The RMP (version 19) is updated accordingly

17.4.7. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0095, Orphan

Applicant: Celgene Europe Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of the final results for study CC-5013-PASS-001 (listed as a category 3 study in the RMP): a non-interventional, observational PASS in subjects treated with lenalidomide to further characterise the safety profile of lenalidomide plus dexamethasone in the treatment of relapsed and/or refractory (R/R) multiple myeloma (MM) in a real-world setting

17.4.8. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/II/0055

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final study report for study 16171, a non-interventional PASS listed as a category 3 study in the RMP (MEA 019): an observational post-authorisation safety specialist cohort event monitoring study (SCEM) to monitor the safety and utilisation of rivaroxaban (Xarelto) for the prevention of stroke in patients with atrial fibrillation (AF), treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and the prevention of recurrent DVT and PE in the secondary care setting in England and Wales (ROSE study)

17.4.9. Trastuzumab - HERCEPTIN (CAP) - EMEA/H/C/000278/II/0135

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report for study BO20652 (OHERA): a non-interventional study aimed to determine the incidence of symptomatic congestive heart failure and cardiac death in patients with human epidermal growth factor 2 (HER2)-positive early breast cancer treated with Herceptin (trastuzumab) as per routine clinical practice. This study is listed as a category 3 study in the RMP. The RMP (version 18.0) is updated accordingly

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[82]

17.5.1. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/MEA 005.4

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

[82] In line with the revised variations regulation for any submission before 4 August 2013

Scope: Annual reports from rheumatoid arthritis registries from the US National Databank of Rheumatic Diseases (RA0005), German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (RA0020), Register for Antirheumatic Therapies in Sweden (ARTIS) (RA0021), British Society for Rheumatology Biologicals Register (BSRBR) (RA0022)

17.5.2. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 006.2

Applicant: Hexal AG

PRAC Rapporteur: Patrick Batty

Scope: Sixth annual interim safety report for study EP006-401: safety follow-up of severe chronic neutropenia (SCN) patients included in phase IV study: safety data collected via cooperation with the Severe Chronic Neutropenia International Registry and reported annually. Patients are followed-up for a total of five years (one year in the SCN study and four years within the registry) [final clinical study report (CSR) due date: 31/12/2019]

17.5.3. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 007.3

Applicant: Hexal AG

PRAC Rapporteur: Patrick Batty

Scope: Sixth annual interim result for study EP06-501: a non-interventional, prospective, long-term safety data collection for Filgrastim Hexal and Zarzio in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell mobilisation (SMART) [final clinical study report (CSR) due date: 31/12/2019]

17.5.4. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 006.2

Applicant: Sandoz GmbH

PRAC Rapporteur: Patrick Batty

Scope: Sixth annual interim safety report for study EP006-401: safety follow-up of severe chronic neutropenia (SCN) patients included in phase IV study: safety data collected via cooperation with the Severe Chronic Neutropenia International Registry and reported annually. Patients are followed-up for a total of five years (one year in the SCN study and four years within the registry) [final clinical study report (CSR) due date: 31/12/2019]

17.5.5. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.3

Applicant: Sandoz GmbH

PRAC Rapporteur: Patrick Batty

Scope: Sixth annual interim result for study EP06-501: a non-interventional, prospective, long-term safety data collection for Filgrastim Hexal and Zarzio in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell mobilisation (SMART) [final clinical study report (CSR) due date: 31/12/2019]

17.5.6. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 012.6

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ghania Chamouni

Scope: Sixth annual interim pooled report for studies D2404 (multinational Gilenya pregnancy exposure registry in multiple sclerosis (MS)), D2403 (a long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started on fingolimod once daily or treated with another approved disease-modifying therapy), D2406 (a long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS newly initiated on fingolimod once daily or treated with another approved disease-modifying therapy) with the first yearly report for study D2409: a long-term, open-label, multicentre study assessing long-term cardiovascular risks in patients treated with fingolimod). This procedure also includes an annual report for the pregnancy intensive monitoring (PRIM) study

17.5.7. Florbetaben (^{18}F) - NEURACEQ (CAP) - EMEA/H/C/002553/MEA 005

Applicant: Piramal Imaging Limited

PRAC Rapporteur: Patrick Batty

Scope: Interim results for PASS study FBB-01_02_13: a prospective observational study to assess the effectiveness of the training and risk minimisation measures recommended for the usage of the diagnostic agent Neuraceq in post-authorisation clinical settings [final clinical study report (CSR): Q1/2019]

17.5.8. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 026.3

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 026.2 [first progress report for study MRK-2859: ulcerative colitis (UC) Nordic registry: a non-interventional observational longitudinal PASS of Simponi in the treatment of UC using Nordic national health registries] as per the request for supplementary information (RSI) adopted in October 2016

17.5.9. Indacaterol, glycopyrronium - ULTIBRO BREEZHALER (CAP) - EMEA/H/C/002679/ANX 002.4; ULUNAR BREEZHALER (CAP) - EMEA/H/C/003875/ANX 003.3; XOTERNA BREEZHALER (CAP) - EMEA/H/C/003755/ANX 002.4

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Third interim report for study CQVA149A2402: a multinational database cohort study to assess RMP specified safety outcomes in association with indacaterol/glycopyrronium bromide in Europe [EU PAS register ENCePP/SDPP/7674]

17.5.10. Rivastigmine - EXELON (CAP) - EMEA/H/C/000169/MEA 036.3

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to MEA 036.2 [Annual interim report (covering the period 1 February 2016 to 31 January 2017) on the effectiveness of risk minimisation measures for multiple patch use with copies of Council for International Organizations of Medical Sciences (CIOMS) reports of medication errors and misuse] as per the request for supplementary information (RSI) adopted in June 2017

17.5.11. Rivastigmine - PROMETAX (CAP) - EMEA/H/C/000255/MEA 037.3

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to MEA 037.2 [Annual interim report (covering the period 1 February 2016 to 31 January 2017) on the effectiveness of risk minimisation measures for multiple patch use with copies of Council for International Organizations of Medical Sciences (CIOMS) reports of medication errors and misuse] as per the request for supplementary information (RSI) adopted in June 2017

17.6. Others

17.6.1. Dexamethasone - OZURDEX (CAP) - EMEA/H/C/001140/MEA 020

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Julie Williams

Scope: Survey to evaluate the physician education component of the simplified Ozurdex (dexamethasone) educational materials in order to assess the effectiveness of the educational material provided to physicians treating patients with Ozurdex by evaluating the physicians' knowledge and understanding of the key information in the Ozurdex injector's guide

17.7. New Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

18. Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments

Based on the review of the available pharmacovigilance data for the medicines listed below and the CHMP Rapporteur's assessment report, the PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no

amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

18.1. Annual reassessments of the marketing authorisation

None

18.2. Conditional renewals of the marketing authorisation

18.2.1. Alectinib - ALECENSA (CAP) - EMEA/H/C/004164/R/0007 (without RMP)

Applicant: Roche Registration Limited

PRAC Rapporteur: Patrick Batty

Scope: Conditional renewal of the marketing authorisation

18.2.2. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - EMEA/H/C/002450/R/0015 (without RMP)

Applicant: Chiesi Farmaceutici S.p.A., ATMP[83]

PRAC Rapporteur: Julie Williams

Scope: Conditional renewal of the marketing authorisation

18.2.3. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0002 (without RMP), Orphan

Applicant: Intercept Pharma Ltd

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus influenzae type B conjugate vaccine (adsorbed) - HEXYON (CAP) - EMEA/H/C/002796/R/0072 (with RMP)

Applicant: Sanofi Pasteur Europe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

[83] Advanced therapy medicinal product

18.3.2. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus influenzae type B conjugate vaccine (adsorbed) - HEXACIMA (CAP) - EMEA/H/C/002702/R/0068 (with RMP)

Applicant: Sanofi Pasteur SA

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.3. Human normal immunoglobulin - PRIVIGEN (CAP) - EMEA/H/C/000831/R/0122 (without RMP)

Applicant: CSL Behring GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.4. Imatinib - IMATINIB ACTAVIS (CAP) - EMEA/H/C/002594/R/0015 (without RMP)

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.5. Memantine - MARIXINO (CAP) - EMEA/H/C/002658/R/0012 (without RMP)

Applicant: Consilient Health Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

18.3.6. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/R/0034 (without RMP)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.7. Ocriplasmin - JETREA (CAP) - EMEA/H/C/002381/R/0033 (without RMP)

Applicant: ThromboGenics NV

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.8. Pertuzumab - PERJETA (CAP) - EMEA/H/C/002547/R/0031 (without RMP)

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

18.3.9. Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)- PREPANDRIX (CAP) - EMEA/H/C/000822/R/0071 (without RMP)

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.10. Telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP) - EMEA/H/C/002676/R/0015 (without RMP)

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Carmela Macchiarulo

Scope: 5-year renewal of the marketing authorisation

18.3.11. Telmisartan, hydrochlorothiazide - TOLUCOMBI (CAP) - EMEA/H/C/002549/R/0020 (without RMP)

Applicant: Krka, d.d., Novo mesto

PRAC Rapporteur: Carmela Macchiarulo

Scope: 5-year renewal of the marketing authorisation

18.3.12. Thalidomide - THALIDOMIDE CELGENE (CAP) - EMEA/H/C/000823/R/0054 (without RMP)

Applicant: Celgene Europe Limited

PRAC Rapporteur: Ghania Chamouni

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 25-29 September 2017 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Daniela Philadelphy	Alternate - via	Austria	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	telephone*			
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Laurence Defays	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	Full involvement
Eva Jirsovà	Member	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Torbjörn Callreus	Alternate	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No participation in discussion, final deliberations and voting on:	3.2.2 Fluoroquinolones for systemic and inhalation use, quinolones for systemic and inhalation use; 6.1.25 Eluxadoline – Truberzi (CAP)
Caroline Laborde	Alternate	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No restrictions applicable to this meeting	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Rhea Fitzgerald	Alternate	Ireland	No restrictions applicable to this meeting	Full involvement
Carmela Macchiarulo	Member	Italy	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Amy Tanti	Member	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in discussion, final deliberations and voting on:	3.2.2. Fluoroquinolones for systemic and inhalation use, quinolones for systemic and inhalation use; 4.1.1. Apixaban – ELIQUIS (CAP); dabigatran – PRADAXA (CAP); edoxaban – LIXIANA (CAP); rivaroxaban – XARELTO (CAP) 4.2.2. Azithromycin (NAP); clarithromycin (NAP); erythromycin (NAP); roxithromycin (NAP) 4.2.4. Desloratadine – AERINAZE (CAP) 7.1.3. Levonorgestrel (NAP)
Kristin Thorseng Kvande	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva	Alternate	Portugal	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Gabriela Jazbec	Alternate	Slovenia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Eva Segovia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Thierry Trenque	Member	Independent scientific expert	No interests declared	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Anna Holubová	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Jana Koprušáková	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Jana Lukačišinová	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Květoslava Mlčochová	Expert - via telephone*	Czech Republic	No restrictions applicable to this meeting	Full involvement
Radim Tobolka	Expert - in person*	Czech Republic	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Tanja Bertelsen Jensen	Expert - via telephone*	Denmark	No interests declared	Full involvement
Pernille Lynge Gammelgaard	Expert - via telephone*	Denmark	No interests declared	Full involvement
Kim Bouillon	Expert - in person*	France	No restrictions applicable to this meeting	Full involvement
Thomas Gruger	Expert - via telephone*	Germany	No interests declared	Full involvement
Kerstin Loeschcke	Expert - via telephone*	Germany	No interests declared	Full involvement
Ellen Pantke	Expert - via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Wiebke Seemann	Expert - via telephone*	Germany	No interests declared	Full involvement
Caitriona Fisher	Expert - via telephone*	Ireland	No interests declared	Full involvement
Emma Lawless	Expert - via telephone*	Ireland	No interests declared	Full involvement
Liana Gross-Martirosyan	Expert - in person*	Netherlands	No interests declared	Full involvement
Cristel Loeb	Expert - in person*	Netherlands	No interests declared	Full involvement
Peter Mol	Expert - in person*	Netherlands	No interests declared	Full involvement
Monika Trojan	Expert - via telephone*	Poland	No restrictions applicable to this meeting	Full involvement
Blanca Garcia Ochoa	Expert - in person*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Rolf Gedeborg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Shazia Khalid	Expert - in person*	United Kingdom	No interests declared	Full involvement
Janet Nooney	Expert - in person*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the agenda topics or activities they participated in

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:
Home>Committees>PRAC>Agendas, minutes and highlights

21. Explanatory notes

The Notes give a brief explanation of relevant minute's items and should be read in conjunction with the minutes.

EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

The RMP describes what is known and not known about the side effects of a medicine and states how these risks will be prevented or minimised in patients. It also includes plans for studies and other activities to gain more knowledge about the safety of the medicine and risk factors for developing side effects. RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available.

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.
PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

A PASS is a study of an authorised medicinal product carried out to obtain further information on its safety, or to measure the effectiveness of risk management measures. The results of a PASS help regulatory agencies to evaluate the safety and benefit-risk profile of a medicine.

Product related pharmacovigilance inspections
(Item 9 of the PRAC minutes)

Inspections carried out by regulatory agencies to ensure that marketing authorisation holders comply with their pharmacovigilance obligations.

More detailed information on the above terms can be found on the EMA website:
http://www.ema.europa.eu/ema